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Original Articles

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1847—CENTENNIAL OF THE ACADEMY—1947

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THE ROLE OF THE ACADEMY IN THE CITY AND THE NATION*

GEORGE BAEHR

President, The New York Academy of Medicine

THIS assembly of the Fellowship and the friends of The New York Academy of Medicine on the occasion of its one hundredth anniversary is gratifying evidence of your appreciation of the Academy's place in the life of the City and of the Nation. It would be regrettable if the high esteem in which the Academy is held were based today in too large a measure upon the things that meet the eye, our magnificent edifice on Fifth Avenue and 103rd Street with its impressive meeting halls and conference rooms, our great medical library, or even upon the high professional and scientific level of the Academy's Fellowship. These are delightful advantages to contemplate and enjoy. But we, Fellows of the Academy, should look upon them rather as symbols of the serious heritage of public responsibility which has been handed on to us by our predecessors over this century.

From small beginnings the Academy has grown through the years to be an indispensable instrument of American medicine. Although its name identifies it with a City, this has become more an indication of its location, for its educational and cultural influences extend through-

* Presidential Discourse delivered at the opening dinner meeting of the Centennial Celebration of The New York Academy of Medicine, March 6, 1947, at the Waldorf-Astoria Hotel, New York City.

out the Nation and even across the seas. Its influence in public health and in the advancement of scientific progress has contributed no small part to the present high standards of medicine in this country. The medical library, one of the largest and most useful in the world, and, in this country, exceeded only by that of the Surgeon General in Washington, now serves six times as many readers as his or, perhaps, any other medical library.

Over these one hundred years, the ideals, the toil and the savings of many distinguished Fellows have been contributed to keep alive the flame of inspiration of the Founders of the Academy through long periods of discouragement. It was their devotion to the public interest over the first three-fourths of a century which eventually won the confidence of the great philanthropic foundations, the Carnegie Corporation and the Rockefeller Foundation and persuaded these and other lay benefactors to come to our assistance in 1923 and help us reach the goal which we celebrate today.

As the fortieth president of the Academy, I shall, therefore, take advantage of this occasion to turn back the pages of history for a few moments in order to review the social and scientific forces at work in the world a century ago, which impelled its Founders to establish this institution. In endeavoring to reconstruct a picture of the times and the influences which motivated the Founders, I am assisted in no small measure by the material which has been assembled during the last two years by Dr. Philip Van Ingen in preparation for a volume on the History of The New York Academy of Medicine, which is to be published in this Centennial year. On behalf of the officers and the Council of the Academy, I gratefully acknowledge our indebtedness to Dr. Van Ingen for the arduous task which he has generously undertaken.

You will recall that the first half of the nineteenth century was characterized by extraordinarily rapid changes in the pattern of American life. Before the year 1800, our country had been a land of farms and hamlets for more than 150 years, and it was the ambition of Jefferson that we should continue to be forever "a nation of husbandmen." Before the end of his second term as President, Jefferson had already revised his views on industrialism under the pressure of changing exigencies. The Embargo of 1807 was followed by a succession of events, the British blockade during the War of 1812, and the subsequent protective tariff, which stimulated industrial undertakings along the Atlan-

tic Coast and greatly accelerated the growth of cities.

The rapidly changing order of the American scene is revealed by the fact that the number of persons engaged in manufactures, and also the number of city dwellers, increased 127 per cent in the twenty years between 1820 and 1840. In 1820, according to Schlesinger, only 5 per cent of the people of this country lived in communities of eight thousand or over; by 1840 the percentage had almost doubled despite the fact that the great drive to the West was helping to preserve the preponderance of agriculture. This wide dispersal of rural populations made conditions throughout the country unfavorable for any close association of physicians, and under this handicap the primitive medical practice of the time, with some notable exceptions such as Mac Dowell, Beaumont and Morton, remained a reflection of the vapid theorizing of the eighteenth century.

In contrast, the rapidly expanding business communities enjoyed the vital advantage of compactness and unity. The new economic life stimulated the establishment of new institutions not only for banking and business but also for general education and medicine. In the growing cities, some of the physicians and surgeons had derived part of their learning and inspiration from the great medical centers of Europe and the British Isles, under such medical pioneers as Louis, Laennec, Dupuytren and Velpeau in France, and Graves, Stokes, Bright, Addison, Hodgkin and Sir Astley Cooper in England, Scotland and Ireland. It is therefore comprehensible that increasing numbers of physicians followed their ambitious lay friends during the early part of the century and forsook rural life for the greater financial and cultural rewards to be found in the rapidly developing urban areas.

These turbulent times witnessed the flowering of American literature, the struggle for public schools, the beginning of the movement for woman's rights and other important humanitarian crusades. The growing intellectual demands of the country are reflected by the fact that in the brief span of twenty years betwen 1820 and 1840, 87 private colleges and 15 state universities were founded. In the year 1800, there were as yet only 5 good medical schools in the entire country, two of them in New York City. Although the number increased rapidly by 1847, inferior or irregular medical schools and medical cults increased disproportionately during this period. Improvement in the general educational level of physicians was further retarded by the fact that the

issuance of a license to practice medicine was the privilege of medical schools. Many were hardly more than finishing schools designed to complete a medical apprenticeship begun under a preceptor. As a result, medical cults and quackery flourished bountifully. In view of the many reform movements of the times, it is, therefore, not surprising that medical leaders in 1846-47 should also have felt the need for decisive action to clear away the debris of intellectual disorder within their ranks and prepare the way for the promising scientific developments which already loomed on the horizon but were not yet clearly visible.

By 1847, American surgeons had become noted for their skill, and there were already promising evidence of Yankee ingenuity in the medical field. Beaumont had made his studies on human gastric physiology in 1825 and ether had been introduced for general anesthesia in Boston in 1846. As the Founders of the Academy perhaps did not realize, 1847 was the momentous year of the publication of Helmholtz' work on the Conservation of Energy wherein was established the First Law of Thermodynamics. This principle, as subsequently extended by the great American, Willard Gibbs, was to make biology and medicine a branch of chemistry and physics. Darwin was as yet only laying the groundwork for the Origin of Species (1859) and Pasteur was beginning to advance slowly and laboriously through crystallography and fermentation to his momentous discoveries in bacteriology, immunology and sanitation.

The first half of the nineteenth century was also the time when Edwin Chadwick, administrator of the Poor Laws of Great Britain, was "making the welkin ring" with his insistent demands that steps be taken by government to prevent the recurring epidemics of disease. It was evident to him that poverty could in large part be prevented by reducing disease and mortality. By 1840, he had finally stimulated the public authorities of Great Britain to action and in 1848, the year after the founding of our Academy, he became the head of the first Board of Health. Chadwick's greatest contribution was his enunciation of the principle that public health measures for the control of disease, unlike the Poor Laws, must be applied for the benefit of all the people. I have no doubt that the great voice of Edwin Chadwick was heard across the seas, and that it played its part in arousing the obvious concern of the young Academy with problems of public health and, more especially, the control of epidemic diseases even though the causes were

unknown at that time and the methods of their transmission were still the subject of bitter controversy.

The same forces and in fact some of the same medical leaders who directed the founding of the Academy were responsible for the almost simultaneous organization of the American Medical Association. In both instances the compelling motives were the need for higher standards of medical education and licensure and for the elimination of charlatanism by the adoption of a code of medical ethics and by public education. The first preliminary meeting for the establishment of a national medical association was held in this City in 1846 at the New York University Medical College under the chairmanship of Dr. Edward Delafield. It was resolved to hold a convention in Philadelphia the following year. In that convention which established the American Medical Association, the newly organized New York Academy of Medicine was represented by the largest delegation, 16 members out of a total of 78 delegates. Our delegation included such men as Delafield, Stearns, Mott, and the Academy's energetic secretary, Campbell Stewart. Not only did the primary incentive for the organization of the American Medical Association come from the State of New York, but at that first official assembly of the Association in Philadelphia in April 1847, the influence of the Academy's 16 representatives was as great as that of the delegates from any of the State Medical Societies or medical colleges.

The founding of the Academy a hundred years ago was inspired by the need for an independent institution in which physicians of high professional standards could find opportunities for mutual improvement and for public service. On November 18, 1846, a sumptuous dinner was held in an elegant saloon at 579 Broadway under the chairmanship of the venerable Dr. Delafield to celebrate the fourth anniversary of the Society for the Relief of the Widows and Orphans of Medical Men. The Society is still active today and its present officers are here tonight to join us in our Centennial celebration. Toward the end of that dinner in the Fall of 1846, being well refreshed with excellent food and wine, the famous surgeon, Dr. Valentine Mott, President of the New York University Medical College, rose and proposed a toast to the older College of Physicians and Surgeons. Not to be outdone, the President of the College of Physicians and Surgeons, Dr. Alexander M. Stevens, rose to return the compliment. Warming up to the occasion, he ended a stirring

address by urging the establishment of a medical hall with ample meeting rooms and a library which would be independent of the medical schools and hospitals and would bring together eminent members of the profession for the purpose of improving the deplorable standards of medical education and medical practice of the time.

After the dinner, forty or more physicians remained behind to discuss these exciting proposals. Dr. John Stearns was voted into the chair, and before this rump meeting adjourned, a committee consisting of Dr. Mott, Dr. Stevens and Dr. Isaac Wood was instructed to call a general meeting of the profession at the Lyceum of Natural History at 561 Broadway "to establish an Academy of Medicine and Surgery and to provide a permanent place for its meetings." Within a few weeks, 185 physicians had enrolled as Founders and at the first formal meeting at the Lyceum on January 13, 1847, the Constitution and By-Laws were adopted, the name New York Academy of Medicine was approved and Dr. John Stearns was elected as the first president. In his inaugural address at the first Stated Meeting of the Academy on February 3rd, Dr. Stearns stated that the purposes of the new institution were "to elevate the standards of medical education, to exclude from our ranks all ignorant pretenders, to enlighten the public mind on the subject of medicine and its collateral branches of science and to take all necessary means to promote the honor, the dignity, the respectability and the usefulness of the medical profession."

In contrast with the high and noble spirit of the enthusiastic Founders, the first home of the Academy was only a rented room over a coal yard at 175 Wooster Street. In spite of an imposing name, Convention Hall, it had space neither for a library nor for the monthly Stated Meetings of the Fellowship. So, during the first 28 years large meetings of the Fellows were held at first at Lyceum Hall on Broadway, for 18 years (1850-1868) in the small Chapel of New York University on Washington Square, and, toward the end of that period, in the lower lecture room of the College of Physicians and Surgeons at 23rd Street and Fourth Avenue.

The medical library, one of the original proposals of Dr. Stevens, was not forgotten. In fact, it was established ceremoniously at the first meeting of the Academy on January 13, 1847 when Dr. Isaac Wood formally presented a copy of Paine's Commentaries in three volumes as the first contribution to the new library. From this small acorn grew

the great oak, but not without weathering many a storm.

At first, the books were kept in the home of the Fellow who had been elected librarian, Dr. Thomas Cock. After Dr. Cock had patiently given the library shelter for 11 years, it was moved for a time to a room adjacent to the library of New York University. But during the Civil War (1865) when the finances of the Academy had sunk almost to insolvency, an increase in the room rent from $7.50 to $12 a month promptly drove the library back to the home of the new librarian, Dr. John Henry Hinton. It was not until 1875 that Fellows and their friends came to the rescue and assisted the Academy in the purchase and remodelling of the first of its own buildings at 12 West 31 Street. Here, the library was housed properly along the walls of the new meeting hall, and its dominant position is indicated by the fact that the new auditorium was named Library Hall.

At first, the work of the Academy, even scientific work, was done through reference to special committees. During the first year, the Academy's concern was largely devoted to the protection of human life and welfare. A review of the activities of the year 1847 is most impressive. Quite appropriately, the very first committee was appointed to procure books for the library, another to investigate and report upon the use of sulfuric ether to mitigate pain in surgical operations and to make experiments on animals; still other committees were appointed in this year to investigate and report upon the subject of sewerage, to carry out investigation on an epidemic of typhus fever, to investigate the importation of adulterated and impure drugs, and (sic!) to study and report upon "the effects upon the human economy of milk from kine tuberculously or otherwise diseased from improper food or confined situations in (these) milk establishments." Although the cause of bovine tuberculosis was still a mystery to the good Founders of the Academy, they were already keenly aware of the hazard to human life involved in the consumption of milk from tuberculous and otherwise diseased cows and intended to do something about it. From these activities of the first year, it is clearly evident that the Founders were among the enlightened medical men of their time. That they were also men of courage and vision is indicated by their very first public actions, a memorial sent to the State Legislature urging the passage of a law for registration of births, deaths and marriages, another to the Congress urging legislation to control the importation of impure drugs, a third to

the State Legislature demanding State responsibility for the care of the feeble-minded.

In January 1848, a Committee on Public Health was appointed to study cholera and other epidemic diseases and to supervise the sanitary condition of the City. In subsequent years came action urging the State to separate medical teaching from medical licensure (1849) and another advocating the passage of a State law which would require that all medical schools be connected with hospitals (1850). There were annual memorials to the Congress which stressed the importance of vital statistics and urged that they be incorporated in the forthcoming Census. This was ultimately accomplished and, although the gathering of the information was imperfect, it represented the first attempt by the federal government to compile any vital statistics. The Academy was also instrumental in collaboration with the medical colleges in eliminating the practice of "body snatching" by aiding passage by the State Legislature in 1851 of the so-called Anatomical Bill which authorized human dissection.

During these early years, scientific papers were read at some of the monthly Stated Meetings, on such subjects as the treatment of ununited fractures, on "Revelations of the Microscope," and upon such extremely controversial matters of the day as the causes of inflammation and the relation of cleanliness of the physician to puerperal fever. On some of these subjects, long, heated discussions were sometimes continued through several successive monthly meetings. In 1850, the work of the Academy was officially subdivided among seven scientific committees but five years later, upon the recommendation of Dr. James Anderson, the By-Laws were again amended and the scientific work of the Academy was divided for the first time into Sections. The present sectional organization of the Academy is therefore 92 years old.

Ten years after it was founded (1857), the Academy made its first major contribution to the reduction of the enormous infant mortality of the time by studying the methods of production and the lasting qualities of concentrated milk. It found them satisfactory and endorsed concentrated milk as a safe and a valuable substitute for the extremely hazardous loose milk of that day and age. In 1861, the Academy called together the first sanitary convention to obtain reform of the laws pertaining to public health in this City and of their administration. This was only the beginning of a long series of annual efforts by the Academy, which

culminated in 1866 in the establishment of a Metropolitan Board of Health, the precursor of our modern Department of Health. Two of the Fellows of the Academy, Willard Parker and John O. Stone, served as the first Commissioners. In later years, when the City Department of Health was established, Commissioners of Health were repeatedly drawn from the Fellowship of the Academy, especially in times of crisis, the most distinguished being Griscom, Bryant, Goldwater, Emerson, and Biggs who served as General Medical Expert. In 1913, Biggs was largely responsible for rewriting the Public Health Laws of the State, which have since been copied by many other States. When the modern State Health Department was established in 1913, he became its first Commissioner, with Dr. Linsly R. Williams, later to be the first Director of the Academy, as his able Deputy.

It can be said with complete justice that Fellows of the Academy played leading roles in the creation in New York State of modern health services which became models for the country, and that the Academy as an institution has been a consistently powerful force in the organization and work of many governmental and voluntary health agencies, local and national, and in their early utilization of new discoveries in the medical sciences for the control of disease and the reduction of mortality. This has been increasingly true since the reestablishment of the Academy's Committee on Public Health Relations 36 years ago, under the Chairmanship of the late Dr. Charles A. Dana. Dr. James Alexander Miller was a charter member of that Committee and has been its Chairman for twelve years. Dr. E. H. L. Corwin has served continuously as its efficient Executive Secretary from the day it started 36 years ago. Under Dr. Miller and Dr. Corwin, the Committee has exercised a great creative influence in the Public Health history of this country. Its recent volume on Preventive Medicine in Modern Medical Practice is used by students in schools of medicine and of public health throughout the land. Its services are recorded in more than 900 reports and publications included in the current centennial exhibit on the History of the Academy in Room 21.

In 1876, the library was opened to the general public and from that time on, by agreement with the City, it has served as the medical part of the New York Public Library system. Later investigations by Academy committees led to improvements in the Croton water supply, in better methods of refuse disposal, in better State care of the insane,

and to at least some improvement of medico-legal testimony. In 1893, impelled by a serious cholera epidemic in the previous year, the Academy took the lead in initiating a successful nationwide movement to eliminate the ineffective quarantine responsibilities of commercially competing seaports and to establish for the first time a national quarantine service. It took years of effort before the Congress was persuaded to enact this obviously necessary legislation. Thirty-three years ago the Academy secured the passage of legislation which abolished the ancient but corrupt and inefficient system of coroners in the City of New York and on its recommendation, an Office of the Chief Medical Examiner consisting of qualified experts was established.

In 1930, in consequence of the inexcusably high maternal death rate, a three year study was begun by a subcommittee of the Committee on Public Health Relations with a paid field staff led by Dr. Ransom Hooker. The Department of Health promptly dispatched to the Academy a photostatic copy of the death certificate of every woman dying in childbirth, and an investigation was immediately instituted at the scene of the labor. The investigation included the family, the environmental conditions and the services of the attending physican, midwife, nurse, relatives and other persons who might have contributed to the result. After three years of patient work, it was found that two-thirds of all deaths in childbirth were preventable and that unnecessary interference or other medical errors by the attending physician was the most important factor in 45 per cent. The publication of these findings aroused a storm of violent criticism; medical societies and physicians in many parts of the country accused the Academy of injuring the reputation of the profession. Today, our county medical societies carefully review and censor the performance of the medical profession in this field. It is no mere coincidence that the maternal death rate dropped more than 66 per cent in the ten years immediately following the publication of the Academy's report. We in New York City can boast that today, about one-fifth as many mothers are lost in childbirth as 15 years ago. Under the influence of the new antibiotics, the decline in very recent years, is, of course, being accelerated. During the year 1946, there was a total of 152,736 live births in the City of New York, yet only 177 women died in childbirth from all causes. If this trend continues, childbirth may ultimately become safer than riding in an automobile or taking a bath!

In 1928, all national societies representing the various branches of medicine and all national governmental agencies concerned with the care of the sick were invited to assemble at the Academy for the purpose of establishing a National Conference on Nomenclature of Disease and preparing a Standard Nomenclature for use in hospitals and medical schools throughout the country. The work, which took 7 years to complete, was carried on within the Academy under its sponsorship, with funds made available to it by the Commonwealth Fund, the major life insurance companies and other philanthropic foundations. Since its publication the Standard Nomenclature of Disease has been adopted by medical schools and hospitals throughout the country and has had a profound influence upon the accuracy of medical terminology and of medical thinking. After the third edition had been issued, the American Medical Association graciously agreed to assume the responsibility for its continuing publication and revision.

In addition to these accomplishments, the medical provisions of the Workmen's Compensation Act of the State were rewritten at the request of the Governor by a Committee under the chairmanship of Dr. Eugene Pool. Through the Academy's Committee on Medical Education, wider educational opportunities have been provided for the continuing education of practicing physicians of the City by weekly practical lectures and demonstrations, by the meetings of the eleven Sections of the Academy, and above all, by the Graduate Fortnight which each year has attracted several thousand physicians. The Academy also serves as the educational information center for visiting physicians from other parts of the country, from Latin America and from overseas. In these postwar years, a special placement center has been conducted for the thousands of medical veterans returning from the Armed Forces who seek fresh educational opportunities in the large voluntary and Municipal hospitals of this metropolis before resuming medical practice.

The Academy's Committee on Medical Information has served for years as the information center for the public on medical matters. During the last two decades it has had a significant influence upon the accuracy of medical reporting by the press and the radio. Its public information bureau and its informative Lectures to the Laity reach many thousands. They are conducted in the tradition of the first anniversary discourse of the Academy delivered by Dr. John W. Francis in the Broadway Tabernacle on November 10, 1847, which attracted an

audience of more than 2500 persons and can be regarded as the Academy's first Lecture to the Laity.

I cannot close without reference to the monumental labors during the past four years of the Committee on Medicine and the Changing Order under the indefatigable leadership of Dr. Malcolm Goodridge and of the Committee's versatile secretary, Dr. Iago Galdston. Within the last two years, the Committee has published a preliminary series of 10 monographs which cover almost all aspects of contemporary problems of medical care. The work of this Committee, which included eminent non-medical and medical leaders, has culminated this month in the publication of a volume embodying its Report and Recommendations on the changes in medical practice and medical education and in the methods of paying for medical care which will be required to make the benefits of modern preventive and curative medicine available to all families of low income. This volume, published by the Commonwealth Fund, is a timely document, for it points the way to far reaching changes which can be made without jeopardizing the high level of performance achieved by American medicine during the last three decades. In my opinion, the work of the Committee on Medicine and the Changing Order represents the pinnacle of the Academy's achievements. Its publication in this Centennial year is a happy and appropriate coincidence.

It should also be a source of pride to the Fellowship that the Secretariat of the World Health Organization of United Nations accepted the hospitality of the Academy last summer immediately following its establishment by a conference of delegates from seventy nations of the world. During the summer and fall of 1946 we were privileged to provide space for the staff of the Interim Commission until permanent headquarters became available. The Academy has therefore had the honor of being the first home of the World Health Organization of United Nations.

It is now important that the Fellowship arrive at an understanding concerning the main lines of activity along which the work of the Academy is hereafter to advance. The Library must maintain its present position as the most useful and influential depository of medical and related scientific literature in the world. This will require the immediate erection of a new building for additional book stacks and reference files, for the Library is now bursting its seams. The overworked library staff must also be materially expanded if the efficiency of their services

to the Fellows and to the public is ever again to equal that of the prewar period. These two objectives will require additions to our present building fund and a substantial increase in endowment. I would remind you that the income from annual dues of the Fellowship at present provides only one-fifth of the operating budget of the Academy and that recent increases in salaries, chiefly of the lowest paid workers, will in 1947, unbalance the rigidly restricted budget by $90,000. To meet these needs, we are entirely dependent upon the generosity of an informed public as well as of the Fellowship.

The second most important future activity of the Academy is in the field of medical education. The continuing education of physicians is a major concern of the Academy, not of the medical schools which are already heavily burdened with undergraduate medical education and with graduate training in the specialties. The great system of voluntary and municipal hospitals of New York at present provides almost one-fifth of all the grade A interneships and residencies of the country. In collaboration with the five medical schools of the City, the Academy will serve as the centralizing agency and will, I hope, assume an even more important role than heretofore in improving the educational curricula of interne and residency training. The interneship and residency period should provide the young physician with an educational and scientific environment in which he can attain his maximum professional and scientific growth. Through its influence upon the hospitals, almost all of whose senior staff members are Fellows, the Academy can in this manner materially influence the future level of medical practice.

The Academy with its exceptional physical and intellectual resources is strategically located in this metropolis to assume, also, an even greater measure of responsibility in the future than in the past for elevating the general level of medical practice through a comprehensive program of continuing education which must follow the interneship and residency training of all physicians until the end of their lives. During the next years, the Academy proposes to weld together the resources of the 65 major hospitals of this great City so as to make it the center of medical education for the physicians of this Nation and of the world. Under the plan we have in mind, New York will become the medical capital as it is already the political capital of the world.

In these educational activities, the eleven clinical and scientific Sections of the Academy must play a more important part than in the past,

each for its own specialty of medicine and surgery. In addition, it will probably be necessary to organize several new Sections devoted to the related basic sciences or to accomplish a closer working relationship with some of the affiliated scientific societies, many of which now meet in the Academy building. At the request of a score of eminent scientists, the Council of the Academy is at present considering the establishment of a new Section on Microbiology which will encompass bacteriology, immunology, parasitology, virology and chemotherapy.

In extending its teaching activities in this manner, the Academy will be required to expand its physical facilities by constructing an addition to the east. This building is to replace the three adjacent tenements on 103rd Street, which we now own. The plans for this extension have been drawn by Mr. Edwin A. Salmon, Chairman of the City Planning Commission. The architectural rendering will be exhibited during March and April in the Academy's Centennial Exhibit on Hospitals in Room A. The proposed exhibit halls will be devoted to visual education through the medium of medical exhibits on matters of vital current importance. These exhibits will be frequently replaced with new material illustrating the most recent advances in medicine and medical technology, and will supplement the didactic and bedside teaching throughout the city. The upper floors of this building are designed to house the staff of the Committee on Medical Education of the Academy through which a city-wide educational program can be administered. In addition to exhibits for the instruction of physicians, the building will also be used from time to time throughout the year for exhibits designed for the education of the general public. The execution of these plans and the erection of the proposed addition will be undertaken as soon as the necessary funds become available for construction of the new addition and for its maintenance. It will require $500,000 for the building and the addition of $1,000,000 to the Academy's endowment.

A third new activity of the Academy has also been approved by the Council. It involves a continuing study of social and environmental factors responsible for illness and mortality, and of the changes in methods of medical practice and medical education which may be necessary before the full benefits of modern curative and preventive medicine can be made available to all the people. With the authorization of the Council, I shall shortly appoint a new Committee on Medicine and the Changing Order for this purpose. This Committee will also concern

itself with preventive psychiatry, social pathology and social medicine, a field which promises to reveal new and ever broader opportunities for public service. Because the terms social pathology and social medicine are still generally misunderstood in this country, we have persuaded Professor John A. Ryle to visit us from across the seas to give us a definition of their meaning and a better understanding of their scope.

A recital of the names of former officers and Fellows who have served the Academy would read like a succession of pages out of the medical history of the country. Following John Stearns, the early presidents included John W. Francis, Valentine Mott, Isaac Wood, Alexander H. Stevens, Thomas Cock, Joseph M. Smith, Willard Parker, John Batchelder, John Watson and James Anderson. After the Civil War came Austin Flint, Samuel S. Purple, B. Fordyce Barker and Abraham Jacobi; then Loomis, Roosa, Bryant and Janeway.

I shall not mention all the distinguished presidents of our own generation except to state that among others, it was Jacobi who saved the Academy during a crucial period 60 years ago when its continued existence was in jeopardy and it was Jacobi and Loomis who later were largely responsible for the erection of our third home on West 43 Street. In addition to Walter B. James, George David Stewart, Samuel A. Brown, it was Bryson Delavan, Arthur B. Duel and our first executive director, Linsly A. Williams who built the beautiful structure which we now occupy, and laid the paths to public service which we now follow. I grieve that Linsly is not with us tonight to share our joy in his accomplishments. Our building is his monument; our deeds will be the measure of our appreciation of his noble character and his life of service to human welfare. I must confess that his great spirit has long been my guide and inspiration.

To these men and to our own beloved Samuel Lambert, John Hartwell and Bernard Sachs, we stand forever indebted. It is with mingled emotions of affection and deep gratitude that, through my inadequate voice, the Fellowship here assembled acknowledges its debt to the past presidents of the Academy who are with us tonight, or are listening to this broadcast, Samuel A. Brown, Eugene Pool, James Alexander Miller, Malcolm Goodridge, Arthur Chace, and to our recent Director, the amiable and efficient Herbert Wilcox. I know that I echo your own feeling of profound admiration when in your name and as an expression of your appreciation, I pledge them our devotion to the aims and ideals of the Academy.

RECENT STUDIES ON THE FUNCTION OF THE ADRENAL CORTEX*

C. N. H. Long

Sterling Professor of Physiological Chemistry of Yale University

THE science of endocrinology is developing in a manner paralleling that of its sister sciences. That is to say from its beginning as merely a description of the phenomena attending the loss or excess of an internal secretion, it is passing by slow degrees to a study of the manner in which these secretions regulate the metabolic processes of the cells upon which they act. For it cannot be too strongly emphasized that the hormones do not initiate new patterns of cellular function, these are an inherent birthright of the cells themselves. All that any hormone does is either to facilitate or inhibit certain types of chemical transformations within the cells. The manner in which this is accomplished remains one of the most fertile fields for further study. Speculation as to the role of hormones in biological processes ranges all the way from the view that they are direct participants in enzyme actions to the more obscure hypothesis that they act as organizers of cellular activity. It is evident, however, that the future development of endocrinology will be inextricably combined with that of our knowledge of the chemical transformations or intermediary metabolism of cells. Indeed it is fair to suggest that "biochemical endocrinology" offers at the present time the most promising field for the elucidation of hormonal activity.

This evening, I have elected to speak on various studies carried out in the last few years to illustrate the value of the biochemical approach to the study of the function of one endocrine gland—the adrenal cortex.

There are three basic questions that require to be answered before we can be said to possess a full understanding of the function of any endocrine organ. These are:

1. What is the chemical nature of the hormones secreted by the gland? To answer this we must proceed from the isolation of the hor-

* Presented at a meeting held under the auspices of the New York Diabetes Association, Inc., on Saturday, January 11, 1947, at Blumenthal Auditorium, Mount Sinai Hospital, New York City.

mone from the gland in pure form, to the determination of its structure. In some instances, this has been followed by the complete or partial synthesis of the active principle. In the case of the protein hormones this last step is still only a future possibility.

2. What are the conditions under which the gland in particular is called upon to secrete increased quantities of its hormone? That is to say what particular circumstances arising within or without the organism require an increased usage of the hormone by the tissues upon which it acts. This question resolves itself into two parts: (a) what is the mechanism, humoral or nervous that activates the secretory processes of the gland, and (b) what are the chemical transformations within the gland that accompany the release or formation of the hormone.

3. In what way does the hormone affect the metabolic activities of the cells upon which it acts? I again repeat that we only recognize the effects of hormones through the alterations they produce in the rate of certain cellular processes. Even such obvious effects as increase in body size, abnormal hirsutism, etc. are of necessity accompanied by metabolic changes. Some of these associated metabolic changes are the most easily recognized evidences of hormonal activity, others are still unknown but we may with some assurance assert that they exist.

In all three of the above categories, chemical nature of the hormone, conditions of secretion and mechanism of action, substantial progress has been made in recent years in our knowledge of the function of the adrenal cortex. Let us now consider these in the above order.

Chemistry of Adrenal Cortical Hormones

The pioneer studies of Stewart and Rogoff, and of Hartman had indicated that various types of adrenal cortical extracts could effect a moderate prolongation of the life of adrenalectomized animals. The recognition that the activity resides primarily in lipid extracts of the gland and that such extracts could indefinitely prolong the life of adrenalectomized animals is to the credit of Swingle and Pfiffner. Their methods of extraction furnished the starting material for all subsequent isolations of the active principles.

These active principles were soon recognized to belong to the great class of chemical substances known as steroids. The isolation of these and some twenty others, not possessing biological activity is due to the

work of Pfiffner, Wintersteiner and Kendall in this country and to that of Reichstein in Switzerland. The wealth of steroid material present in these glands, both in number of compounds and the diversity of their action, exceeds that found in any other organ of the body, not excluding the gonads, which in their capacity as endocrine glands also secrete steroid hormones. Why the adrenal cortex should contain and presumably manufacture not only the steroids with the characteristic activity of this organ, but also those with gonadal activity, as well as a large number with no known biological activity, is but one of the unsolved problems of its function.

The minute concentrations in which the active steroids of the adrenal —the corticosterones—are present in the gland has made it difficult for investigators to carry out the number of experiments with the pure hormones that they have desired. The generosity of those who have laboriously isolated, and then donated these valuable compounds to their colleagues for their work is beyond praise, and as one of the recipients of their kindness I am happy to acknowledge how much it has meant to our work.

It is also a matter of gratification to know that the partial synthesis both of dehydro corticosterone and 11-dehydro-17-hydroxy corticosterone from desoxy cholic acid has now been accomplished. This important work is the result of the collaboration of a number of organic chemists in different parts of the country. The combined efforts of Wallis of Princeton, Kendall of the Mayo Clinic, Gallagher at Chicago, Riegel at Northwestern, Wintersteiner at the Squibb Research Institute and Sarett of the Research Laboratories of the Merck Company have resulted in the preparation of quantities of the synthetic hormones far exceeding those ever available from natural sources. The importance of this to the further conduct of research in the field of adrenal physiology is obvious while the potential value of these new synthetic hormones in the treatment of human disease can now, for the first time, really be explored.

Conditions Associated with Increased Adrenal Cortical Secretion

The manner in which the activity of the adrenal cortex is adjusted to the needs of the organism and the circumstances which call forth an increased secretion of its hormones is a problem engaging many investi-

gators at the present time. As I mentioned above, one of the tenets of present day endocrinology is that the endocrine glands do not act in an independent and haphazard manner but adjust their secretory rate very closely to the actual needs of the moment.

The second question to be answered is: "What are the factors that regulate the secretory activity of this gland?" This requires for its solution the development of methods that will tell us when the gland is actually producing its hormone at an accelerated rate.

As regards this question a good deal of information is now available. In 1930, P. E. Smith showed that removal of the hypophysis in the rat was followed by atrophy of the adrenal cortex and that this could be prevented by the injection of crude pituitary extracts or by implants of the anterior pituitary itself. A large amount of work has since shown that all conditions that cause adrenal cortical enlargement, and these are too numerous to mention, fail to do so in the absence of a factor from the anterior lobe of the pituitary. This factor is a protein hormone now known as the adrenotrophic or corticotrophic hormone. It has recently been isolated from the anterior lobe in a highly purified, if not completely pure form by workers in two laboratories. Such a preparation has been obtained from sheep glands by Li, Simpson and Evans and from hog glands by Sayers, White, and myself.

It is interesting to report that these two groups, working independently and with the pituitaries of different species isolated a substance whose biological, chemical and physical properties agreed in a remarkable manner.

When injected into animals this trophic hormone produces all the effects given by the cortical hormones themselves. Thus it has been found that it brings about an increased level of liver glycogen and of urinary nitrogen excretion. It causes glycosuria, sodium retention, and increased potassium excretion in rats, and has an effect identical with that of the corticosterones in reducing the number of circulating lymphocytes. All these effects can be evoked in the hypophysectomized animal in which no other known agent will cause an increased adrenal cortical secretion. So far as is known at the present time the only effect of this hormone is the stimulation of the secretory function of the adrenal cortex.

However, while the identification and isolation of this trophic hormone answers the question as to the agent responsible for an increased

adrenal cortical secretion it merely transfers to the anterior lobe of the pituitary the question as to the mechanisms that cause this gland to secrete the agent that is essential for an increased hormone production by the adrenal cortex. Are these mechanisms of nervous or humoral origin?

Before such a question can be experimentally tested it is necessary to have available some method of determining the rate of secretion of the adrenal cortical hormones. When we began our studies the available methods for following adrenal cortical secretion were not very suitable for studies in which small animals were to be exposed to a variety of conditions. Those that had been used included (a) the determination of "cortin" excretion in the urine by chemical or biological methods. This is obviously impracticable in small animals although in man it has been successfully used by Browne and Venning and others to show that trauma or infections increase the secretory rate. (b) Direct determinations of cortical hormone by biological methods in the blood of the adrenal vein. This method, applicable only to dogs under anesthesia, had been used by Vogt in England. It has yielded important information including the demonstration that epinephrine injection or the administration of glucose forming but not non-glucose forming amino acids is followed by an enhanced output of the hormone. (c) Methods based on the actual content of hormone in the gland. These are not practical at the present time.

Consideration of the question led to the suggestion that some lipid constituent of the gland might vary with different degrees of its activity. It was known that the stainable lipid of the gland decreased under conditions associated with increased secretion, also there was some evidence that the cholesterol content of the gland underwent similar changes. Indeed, there was a voluminous literature on this last subject, containing many contradictions and expressions of opinion as to the relation of adrenal cholesterol to the intermediary metabolism of this substance in the rest of the organism. The general idea that cholesterol might be the precursor of the steroid hormones has also been put forth by various investigators but curiously enough no experiments to demonstate that it varied under conditions of increased secretion of the adrenal cortex or gonads had been done.

We, therefore, injected the highly purified preparations of adrenotrophic hormone into rats and determined the cholesterol content of

the glands after various intervals of time. It was found that single injections of this trophic hormone decreased the cholesterol content of the adrenal by some 50 per cent in three to six hours, while its return to normal levels required many hours. Similar results were observed in hypophysectomized rats, provided too long a time had not elapsed since the operation. The cholesterol content of a variety of other tissues was not affected by such injections. As will be seen later, exposure of animals to such stresses as cold, burns, trauma or hemorrhage brought about similar alterations in the adrenal cholesterol of normal rats but did not alter the level in hypophysectomized animals. Evidently the natural secretion of adrenotrophic hormone following such procedures can also be detected by the changes in the cholesterol content of the adrenal.

In reviewing these results it appeared entirely possible that the rather long period, an hour or more before the adrenal cholesterol fell significantly, might be due to the fact that this substance acted as a reservoir for the continual replenishment of the hormone itself and that other substances in the gland might be more closely related to the actual secretion.

The adrenal cortex is also unique in its high content of ascorbic acid (Vitamin C). Furthermore, this gland and the corpus luteum are the only tissues in which such a high concentration of the vitamin is found along with a very high concentration of cholesterol in the ester form. It is unnecessary to remind you that ascorbic acid was originally isolated from the adrenal although the reasons for its presence in such large amounts were not known. Further study of the literature indicated that as in the case of cholesterol the level of this vitamin in the adrenal was subject to wide variations, it being notable that under conditions of stress low values were found.

Consequently, similar experiments were carried out with adrenotrophic hormone and it was found that the ascorbic acid level of the adrenal fell very promptly after the injection, reaching values of less than 50 per cent of the original level within one hour. Indeed, a significant decline could be detected within 20 minutes after injection. Exposure of normal animals to the types of stress mentioned above was followed by marked reductions in adrenal ascorbic acid yet similar treatment of hypophysectomized animals failed to affect the level of the vitamin in the gland. The ascorbic acid content of other tissues

was not affected either by adrenotrophic hormone or by exposure of animals to conditions that were followed by a decline in its content in the adrenal.

While it might be argued that these changes in adrenal cholesterol and ascorbic acid are only indirect measure of adrenal cortical secretion, our experience has convinced us that they furnish a reliable and rapid indicator of this secretion. As I have pointed out above, it is apparently mediated by the preliminary passage into the blood stream of additional quantities of the pituitary adrenotrophic hormone. Even if these changes in adrenal choleserol and ascorbic acid were not directly associated with the elaboration and secretion of the cortical hormones but were merely expressions of a general heightening of adrenal metabolism, they would still be of value for following the secretory activity of the gland. However. there is other evidence that more directly links these changes in adrenal chemistry with the actual formation and release of the cortical steroids. Bloch and Rittenberg have shown by the use of cholesterol tagged with deuterium that not only the bile acids but also progesterone are formed with this steroid. The structure of progesterone is sufficiently akin to that of the corticosterones to make it extremely probable that the latter also are formed from cholesterol.

At least one role of ascorbic acid in the adrenal would appear to have been clarified by the recent report of Lowenstein and Zwemer that it is possible to isolate from this gland a water soluble and biologically active steroid in which the steroid nucleus is apparently linked to ascorbic acid. If this is correct then ascorbic acid is actually a part of the hormone in the form in which it is secreted by the gland, cholesterol presumably furnishing the material from which further quantities of the steroid portion may be elaborated as it is required.

The association of a vitamin with a hormone in this manner is the first known example of a common point of activity of members of these two important groups of substances, although examples of vitamins forming portions of co-enzymes are now fairly numerous. The recent report of Price, Colowick, and Cori on the influence of insulin, anterior pituitary and cortical hormones on the activity of the enzyme hexokinase is an outstanding instance of such interplay, particularly since nicotinic acid amide is a component of the hexokinase system. In this system, a hormone, vitamin and protein enzyme are all part of a cellular mechanism for carbohydrate metabolism.

Finally, it may be pointed out that there is an excellent degree of correlation between the decline in adrenal cholesterol and ascorbic acid and such tangible and well authenticated manifestations of adrenal cortical activity as the increase in liver glycogen in fasting animals and the fall in the number of circulating lymphocytes.

It is, therefore, possible not only to use these changes in the chemical composition of the adrenal as indicators of increased secretory activity but also under the right conditions to employ them as a method for the assay of the adrenotrophic hormone itself. For this last purpose it is desirable to use hypophysectomized animals as the test objects since their adrenal cholesterol and ascorbic acid will only be affected by the trophic hormone and not by any non-specific agent in the material injected. By the use of such a method Dr. and Mrs. Sayers have found that a rat pituitary gland contains about 20 micrograms of the hormone. It should now be possible to apply this method to the determination of the level of adrenotrophic hormone in the body fluids, a procedure that should be of particular value in the diagnosis of certain endocrine disorders in man.

We have already made a considerable number of observations on the effect of various procedures on the secretory activity of the adrenal cortex. In most of these experiments we have been satisfied to determine only ascorbic acid since it reflects any change more rapidly than cholesterol. We have found that exposure to cold (4° C. for one hour) hemorrhage, trauma to muscles, and particularly to the long bones, painful stimuli, cutting or bruising the skin, burns, the intraperitoneal injection of cold isotonic saline or other fluids, and the inhalation of volatile anesthetics, all cause an immediate and prompt increased rate of secretion of the cortical hormones. As might be expected the degree of activation of the gland is determined by the intensity and duration of the stimulus applied.

We come now to an interesting and important point concerning the manner in which these diverse types of stimuli bring about an increased degree of cortical secretion. Three recent investigations bear on this point.

(a) We have found that epinephrine which is certainly released after the most varied types of stress, causes within an hour after subcutaneous or intravenous injection a decrease in adrenal ascorbic acid in normal rats but not in rats 3 days after hypophysectomy. The

amounts required are within the physiological range.

(b) Vogt also has found that epinephrine causes a marked increase in the quantity of cortical hormone in the adrenal vein blood of dogs. However, in one experiment on a decapitated dog she reports that epinephrine also caused an increase and in a private communication she informs me that it also augments the output of the isolated, perfused adrenal of the dog. Nevertheless, in chronic experiments, epinephrine produced adrenal hypertrophy only in normal but not in hypophysectomized rats.

She concludes that the effect of epinephrine is a direct one on the secretory cells, independent of the anterior lobe and that the absence of an effect of epinephrine in rats injected from the 3rd to the 12th day after hypophysectomy is due to the degeneration of the glands caused by lack of corticotrophic hormone.

In other words Vogt and ourselves are agreed that epinephrine is a potent stimulus to adrenal cortical secretion, although we differ as to its mode of action.

It is possible to devise more decisive experiments to settle this point but whatever may be the answer it is of importance that either directly, or indirectly through the adrenotrophic hormone, the stimulation of the sympathetic nervous system and consequent liberation of epinephrine is capable of increasing cortical hormone output. Such sympathetic activity is always a component of these varied circumstances that are known to call forth such secretion by the cortex. Heat, cold, hemorrhage, trauma, burns, toxic agents, and painful stimuli of all kinds are always associated with an increased degree of activity of the sympathetic nervous system. Consequently it may be assumed that this is at least a very important if not the only means by which an augmented supply of cortical hormone is released to meet these states of emergency.

I am also aware of the implications of the statement that epinephrine can cause stimulation of the adrenotrophic function of the anterior pituitary. For if it is an agent in this regard then it must act either by the stimulation of adrenergic cells in the anterior lobe, nerve cells whose existence is equivocal, or directly upon certain sensitive cells in the gland itself, after the manner in which it accelerates glycogenolysis in skeletal muscle.

(c) A third set of experiments expressing another point of view. or rather another mechanism by which adrenal cortical secretion is regu-

lated has recently been published by Dr. and Mrs. Sayers.

They have found that prior treatment of rats with cortical hormone prevents the usual fall in ascorbic acid when the animals are exposed to cold. We have confirmed this and shown that such treatment also prevents the fall in adrenal ascorbic acid not only after painful stimuli, trauma. etc., but also that usually produced by epinephrine. I have no doubt that the effect of other types of stress on this component of the adrenal can also be prevented by prior treatment with cortical hormone. Sayers and Sayers suggest that the blood level of cortical hormone determines the secretion of the adrenotrophic hormone. A decline in the former, presumably caused by the stress applied to the animal acts as a stimulus to the secretion of the latter. If the fall in the blood level of cortical hormone is prevented by injection of exogenous cortical hormone, then the pituitary does not respond. In other words, a differential and temporary hypophysectomy is achieved by this means.

These experiments imply that stress produces conditions that cause an increased rate of utilization of cortical hormone in the tissues. This in turn brings about a reduction of the blood level of this hormone which is the exciting factor to the anterior pituitary. Such a view is perhaps half way between that of Vogt and ourselves. It regards the adrenotrophic hormone as the essential factor for cortical secretion but relegates epinephrine to a place with other non-specific types of stress that reduce the blood level of cortical hormones. Although our experiments indicate that the stimulating effect of epinephrine on the pituitary (if this exists) is abolished by raising the blood level of cortical hormones, it must be remembered that epinephrine itself is a hormone with well defined points of action and is not in the usual sense "a non-specific agent." However, it is also possible that the well known metabolic effects of epinephrine may cause an increased utilization of cortical hormone by the tissues or change the composition of the blood passing through the anterior lobe. Only further experimentation can settle these controversial points but I again repeat that the fact that epinephrine, by whatever mechanism, increases the secretion of cortical hormone is in itself a point of some importance in our understanding of the means by which the organism adapts itself to stress. Indeed this observation furnishes an interesting corollary to the emergency theory of adrenal medullary function put forward by the late W. B. Cannon.

Even with these points unsettled the picture of the control of

adrenal cortical secretion appears at the present time to be as follows:

(a) The changes in adrenal ascorbic acid and cholesterol may be used as indicators of cortical activity. The former is probably directly related to the secretion of the hormone, the latter acting as a reservoir of the precursor of the hormone.

(b) The various circumstances that increase the cortical secretion do so in all probability by first activating the adrenotrophic secretion of the anterior pituitary.

(c) The manner in which anterior lobe activation is affected is either by a decrease in the blood level of cortical hormone or some other unknown changes in the composition of the blood traversing the gland.

(d) The release of epinephrine, which occurs in so many circumstances, increases adrenal cortical secretion. It may do so (1) either by a direct effect on the gland (which is Vogt's view), (2) by stimulation of the anterior pituitary, (3) as a result of its own effects on the composition of the blood passing through the pituitary.

The series of events just outlined is a good example of the correlation and interplay of three components of the endocrine system, anterior pituitary, adrenal cortex and medulla. Their combined operation facilitates the adaptation of the organism to external and internal stresses, stresses which if unchecked would threaten its continued existence. Their operation not only corrects changes in the fluid environment that are detrimental to cellular function but also creates conditions within the environment and the cells that are best adapted to meet the emergency.

Mechanism of Action of Adrenal Cortical Hormones

I would now like to turn from a consideration of the regulation of adrenal cortical activity to the equally complicated question as to the manner in which the hormones of this gland produce the observed metabolic changes in the cells and body fluids. For it must be in their capacity to facilitate certain types of cellular activity that the protective properties of these hormones reside.

This evening, I have not time, nor do you have the physical endurance. to listen while I review the large amount of work that has been done on the function of the cortical hormones. I can but remind you that these hormones are particularly active in the regulation of many

phases of metabolism. Thus, they regulate the sodium, potassium and water balance by their influence on the rate of kidney tubular excretion and reabsorption of these ions and in this way control the shift of fluid and electrolytes between the various compartments of the body. As is now well known these hormones also have a marked effect on several phases of the organic metabolism. It was recognized many years ago that a subnormal blood glucose level is a frequent finding in adrenal insufficiency in animals and man. Britton has shown that the other carbohydrate constituents of the body, notably the liver and muscle glycogen are depleted and that the injections of the cortical hormone, even without food rapidly restores these levels.

In spite of this. it was soon surmised that neither the control of the electrolyte or carbohydrate levels fully explained the action of the hormone. For while it is true that adrenalectomized animals or humans with adrenal insufficiency might die from electrolyte loss or carbohydrate depletion, the mere administration of sodium salts or carbohydrate was not sufficient to return them to a normal state, even though life might be extended by their use.

In 1934 Lukens and I found that adrenalectomy alleviated many of the consequences of total pancreatectomy in the cat and dog. The most notable effect, apart from a prolongation of life was the reduction in urinary glucose and nitrogen excretion, a fall from the characteristically high to more normal blood glucose levels and a striking abatement of ketosis.

The general conclusion concerning these metabolic changes was that adrenalectomy reduced the high rate of conversion of tissue proteins to glucose (gluconeogenesis) while at the same time it allowed a higher rate of carbohydrate utilization. The converse conclusion would be that the adrenal cortical hormones accelerated the conversion of tissue proteins to glucose and/or inhibits carbohydrate utilization by the tissues. Indeed, Vogt has recently shown that infusion of amino acids forming glucose in the body increased the requirement for cortical hormone but the non-glucose forming amino acids do not.

Later experiments demonstrated that in other conditions accompanied by a high rate of gluconeogenesis from protein, adrenalectomy was followed by a comparable reduction in the quantity of protein undergoing catabolism. It has since been shown in several laboratories besides our own, that the injection of either the cortical steroids or adreno-

trophic hormone into normal fasting animals increases the rate of protein breakdown to a marked degree, while at the same time, large quantities of glycogen are deposited in the liver. In fed animals, as Ingle has shown, actual glycosuria follows prolonged injection of either of these hormones, indicating that carbohydrate utilization was also suppressed.

The adrenal cortical hormones by their capacity to accelerate the catabolic phases of protein metabolism retard the growth of growing animals. They. therefore, stand in opposition to the growth promoting factor of the pituitary, which promotes the retention of protein in the body. Since the activities of the adrenal cortex is also regulated by the anterior pituitary, this gland exercises control over the rate of both the catabolism and anabolism of protein.

However, it will be appreciated that though we use such terms as "promotion of gluconeogenesis," "stimulation of protein catabolism," "inhibition of carbohydrate utilization" to describe the function of the adrenal cortex, we have not yet succeeded in completely defining the action of these hormones. It is true that a stimulation of glucose formation along with a suppression of tissue utilization of carbohydrate is an important factor during periods of fasting. Furthermore the present concept of a dynamic state of protein metabolism indicates the necessity for the regulation of catabolism as well as anabolism. In spite of all these examples of the teleological significance of the hormone there is still one feature of adrenalectomized animals that requires consideration before we can accept any present hypothesis as a complete explanation of the function of this gland. This is the remarkable inability of adrenalectomized animals to withstand alterations in the external or internal environment that are easily tolerated by intact animals. This intoleranc is too well known to need further description but it should be remembered that merely correcting the disturbances in the sodium or carbohydrate metabolism by administration of these substances is not sufficient in itself to insure survival.

These measures while they may bring about the extended survival of adrenalectomized animals living under quiet undisturbed conditions of existence, fail conspicuously to protect such animals under conditions which are easily tolerated by normal animals. Only the cortical hormones can confer a normal resistance to stress to either adrenalectomized or hypophysectomized animals.

This fact and many more that might be enumerated, for example

the effect of the hormones on the early fatigue of the skeletal muscles, so well described by Ingle. indicate that there still remains to be found some other basic mechanism of their action. The effects of adrenal cortical insufficiency are extended to many organs, each of which expresses this insufficiency in terms of its inherent function. Thus we observe the rapid fatigue of working muscles, inadequate intestinal absorption, reduced ability of the kidney to separate sodium and potassium, and such defects in liver function as a decreased rate of gluconeogenesis. Yet even with such evidence of the necessity of cortical hormones for the proper function of so many different organs we must assume, until it is proved otherwise, that in each organ the point of action of the hormones is the same. At the moment we do not know, except in general terms, what this effect is. All we can say is that without these hormones the capacity of many types of cells to perform their particular function is impaired, and that this becomes particularly evident in times of stress.

Recently some new observations on a well known effect of cortical hormones have been reported which indicate, if further proof were needed, that we have still much to learn about their action in the body.

Those of you who are familiar with the beautifully illustrated monograph by Thomas Addison in which was first clearly defined the relationship of the adrenals to the disease in man which now bears his name, will remember that one plate shows the remarkable enlargement of the abdominal lymph nodes in the cases he described.

Since that time, numerous observations both in man and animals have made us aware of the reciprocal relationship between the adrenal cortex and the lymphoid elements of the body. Withdrawal of the hormone is associated with lymphoid enlargement; an excess of hormone causes rapid involution of these elements. This relationship has been particularly emphasized by Selye in his many papers describing the phenomena associated with the "alarm reaction." This investigator has shown that a variety of insults to the organism cause, along with adrenal cortical hypertrophy, a rapid involution of the thymus and lymph nodes.

Dr. White in my laboratory* in association with Dr. Dougherty of the Department of Anatomy at Yale have recently made a more detailed analysis of this relationship. Their results may be summed up as follows:

* The investigations reported in this paper from the Yale Laboratories were supported by a grant from the Fluid Research Fund of the Yale University School of Medicine.

(a) The number of circulating lymphocytes is under pituitary-adrenal control. That is to say that when the cortical hormones or the adrenotrophic hormone is injected into normal animals they cause a rapid decrease in the blood lymphocytes reaching a maximum a few hours after injection.

(b) The reduction in the blood lymphocytes is not due to an increased rate of withdrawal by the tissues but is brought about by a rapid lympholysis in the lymphoid tissues themselves. This is further emphasized by the experiments of Reinhart who found a 50 per cent reduction of lymphocytes in the thoracic duct lymph within twenty minutes after the injection of adrenotrophic hormone.

(c) This lympholysis liberates into the lymph and ultimately into the blood serum the contents of the lymph cells. One of these constituents has been identified as normal serum gamma globulin, a second is probably serum beta globulin. The rise in total serum globulin, due almost entirely to these two globulins has been shown by electrophoresis of the serum of treated animals.

These experiments indicate an entirely new effect of cortical hormones on protein metabolism. For by this action, intact cellular protein molecules are translocated through the body fluids to all parts of the organism. As in all instances of hormone action this process is not initiated by the hormone but merely altered in the rate at which it proceeds. Once dispersed in this manner this protein may be metabolized by the different tissues in a manner best suited to their requirements; these presumably vary according to their function.

(d) Since it is well known that the gamma globulins are the fraction of the serum proteins that carry the specific immune bodies, White and Dougherty immunized animals to various antigens both with and without the injection of cortical hormones. In all cases the titre of the specific antibodies in the serum rose faster and to higher levels in the group receiving the hormone. But this was not all. For if the injection of both hormone and antigen was stopped and sufficient time allowed for the serum titre of antibody to largely disappear, the injection of a single dose of cortical hormone caused in a few hours, antibodies to reappear in the serum to levels reached during the height of immunization. Exposure of immunized animals to any stimulus that causes adrenal cortical secretion was followed by similar rapid increases in serum antibodies. In other words this "anamnestic reaction" is a mani-

festation of the control of lympholysis and serum globulin release by the cortical hormones.

It is apparent that the release of immune globulins in immunized animals is merely a special case of a general phenomenon, for similar quantities of non-immune globulins are released along with other cellular materials from the lymphocytes of non-immunized animals. Yet in the immunized animals, the actual release of cortical hormones confers a specific resistance to a particular infecting agent. Is there then a relationship between the lympholysis occurring in non-immunized animals and their resistance to such non-specific stimuli as heat, cold, trauma, etc.? Is such non-specific resistance determined, at least in part by the capacity of the cortical hormones to liberate from the lymphoid elements into the circulating fluids substances that are vital to the cells for a successful defence against the distortion of their internal environment? This is an unanswered but important question but these experiments have opened an entirely new line of thought not only concerning the inability of adrenalectomized or hypophysectomized animals to contend with the factors that distort their internal environment, but also as to the mechanism of action of the cortical hormones. If nothing else they lend emphasis to the point that there are still unexplored fields in our knowledge of the function of the adrenal cortex.

Discussion

Dr. Robert F. Loeb: I think we are all very priveleged to have heard a most stimulating and provocative talk by Dr. Long. I think the most important thing is that we congratulate him and his coworkers on the contributions which they made to our understanding of the functions of the adrenal cortex. Anything which I might say after this is pretty much of an anticlimax. but I will make my climax very brief.

There is one point which Dr. Long introduced early in his talk which I should like to emphasize very strongly and that is the question of just what the role of the endocrine glands may be. We are all pretty much interested in them these days, and I think he put his finger on a very important point when he emphasized that they function primarily to facilitate or inhibit certain cell activity and probably not to be primary regulators.

I believe it is terribly important for us to remember that even the

lowly malarial parasite has a perfectly good anaerobic and aerobic glycolytic cycle which my friends tell me they cannot distinguish from that of man, and yet to the best of my knowledge, the malariologists do not associate a pancreas, a pituitary and a duodenum with the malarial parasite. Still it carries on. It grows, oxidizes and divides without an endocrine system, and perhaps it is well to look on the endocrine system as a very important superstructure which is introduced as an expediting system, as Dr. Long has said, to facilitate or inhibt certain fundamental activities in a very complicated organization of society of cells such as exists in higher animals.

One of the other very important, very exciting parts of this work, to say nothing of the work concerning the potentialities for measuring concentrations of hormone in blood, at the present time is what Dr. Long emphasized, namely, the opening up of a vista concerning the interrelationship of the hormones and vitamins, the central nervous system for instance and the enzyme systems themselves. It seems to me that if one is going to strike at the heart of the problem of the hormones that more work must be directed towards this end.

The clinician has one point, which I should like to emphasize too, and that is, I think in certain ways we have harder times than do the biochemists and physiologists. They work with small animals. We work with the large one. We all know the importance and easily demonstrated factors of protein-carbohydrate disturbances in animals and the response of small animals to the administration of the 11-oxy- or 17-hydroxysteroids. In man in Addison's disease we certainly see manifestations of the profound disturbance in protein-carbohydrate metabolism as seen in animals in Addison's disease. They are a counterpart of the opposite end of the spectrum. We see evidence of overactivity of these same substances in Cushing's syndrome. Yet what bothers me terribly is the fact that even with the administration of this new synthetic 11-dehydrocorticosterone, which Dr. Long mentioned, given up to as much as 100 milligrams a day we found preciously little in the way of objective evidence of activity. Some reports have come out indicating some increased nitrogen excretion but I think even those have not been as dramatic as one might have expected.

Perhaps the whole answer to this is to be found in a quantitative rather than in any other difference in animals. Perhaps the studies of Martha Vogt may point the way to that.

As you probably all know, in her assay of the blood from the adrenal vein, I think of 10 kg. dogs under nembutal anesthesia, she calculates that approximately 250 cc. of a good commercial extract is elaborated in a day, and it is possible that one of the reasons why we don't see more dramatic effects in man as they are seen in small animals of this type may be purely the quantitative problem.

Finally, I do think that I should like to share Dr. Long's feeling that while tremendous advances have been made in our understanding of the adrenal cortex, there are still some questions which call for solution. I should once more like to express my appreciation to Dr. Long.

DR. LOUIS J. SOFFER: I recall in 1928,or 1930, when it was originally pointed out that the adrenal cortex represented a storehouse for considerable quantities of ascorbic acid. Those of us who are interested in the experimental and clinical study of the cortical insufficiency all thought essentially in the same terms, that it would be worth while seeing the effect of the use of large amounts of ascorbic acid in the treatment of the bilateral adrenalectomized animal and in patients with Addison's disease. You probably know that the results were entirely negative, that the administration of ascorbic acid to the adrenalectomized animal in no way supplements the effect of whole adrenal extract, so if ascorbic acid plays any role in the manufacture of adrenal cortical extract such role can be played only in the presence of intact adrenals. Apparently no other organ in the body is capable of exerting that function.

I was particularly intrigued with the studies of Dr. Long and Dr. Sayers on the effect of epinephrine on anterior pituitary stimulation.

The history of epinephrine too is a very interesting one. When Dr. Abel succeeded in crystallizing epinephrine in the early nineteen hundreds, a good deal of investigative attention was concentrated on the study of the pharmacology and significance of epinephrine. For two decades or more all investigative work was conducted with epinephrine and we really did not think so much in terms of the possibility of other hormone secretions on the part of the adrenal. Finally, when it was realized that the epinephrine by no means represented the only hormone elaborated by the adrenal and attention concentrated on other hormones secreted by the adrenal cortex, I think interest was lost sight of in relation to epinephrine, and this work of Dr. Long represents an awakening of the possible significance of epinephrine.

The fact that epinephrine can be injected and can stimulate the anterior pituitary with the formation of adrenotrophic factor is an important one. In our own laboratory, along somewhat similar lines, we found the injection of epinephrine into intact animals resulted in the secretion of relatively large amounts of thyrotrophic factor and these large amounts are formed in the intact animal, formed in the thyroidectomized animal and formed in the adrenalectomized animal. Curiously enough, in the intact animal the injection of epinephrine eventually loses its effect because of the development of inhibitory mechanism.

On further investigation it was found this inhibitory mechanism is probably related to the adrenal cortex because the inhibitory mechanism does not develop in the adrenalectomized animal, and is promptly manifested again in the event of the injection of whole adrenal cortical extracts. So we see the pendulum swinging back again and epinephrine is beginning to assume a much more important role in adrenal cortical physiology than we had originally suspected or anticipated.

It may be the epinephrine and the sympathetic nervous system act as a trigger mechanism which sets off complete byplay of pituitary function which stimulates the adrenal. Of course if we assume that epinephrine is capable of stimulating the anterior pituitary with the elaboration of adrenotrophic and thyrotrophic factor, it sheds a new light on the carbohydrate function of epinephrine and no longer can we think of it in terms of glycolytic effect but think of it in the larger sense in which it has an extensive effect on the carbohydrate metabolism related in part to the stimulation of the pituitary with the formation of adrenotrophic factor and the effect on the carbohydrate-protein metabolism, and the decrease in the peripheral utilization of carbohydrate.

I agree too with Dr. Long and Dr. Loeb that we are really entering into a new era in endocrine physiology, in endocrine biochemistry, and to those of us who are interested in adreno-cortical physiology, there are many problems which are yet to be solved.

Dr. I. Arthur Mirsky: The third discusser usually feels very insignificant, very definitely out of place, because he has to anticipate what the first two are going to say. That is rather difficult on a precise subject of this sort.

Interestingly enough, I did find an aspect which I thought perhaps nobody might mention. I was fascinated to note, like Claude Bernard,

Cannon and other real students of biology, Dr. Long has drawn our attention to the need for viewing a particular problem not from a very precise point of view but from the point of view of the total organism. His data and deductions lead directly to the consideration of the mechanism whereby the organism maintains a constant in terms of Claude Bernard's "milieu intereus" or homeostasis. He has shown us how the adrenal cortex and its products play an essential role in physiologic integrations and demonstrated the manner in which they are affected by disease processes, and how disease processes are affected by them.

It has been known for some time that the pituitary has a dual function in protein metabolism. Studies from our laboratories suggested that the anabolic aspect of pituitary function was due to pancreatrophic effect, a conclusion with which Young and more recently Ogilvie are in accord. However, it was the studies of Long and his group which gave us an understanding and explanation of the catabolic effects of the pituitary, that is, the effect through the adrenal cortex. The recent studies of Cori on the inhibition of the isolated system hexokinase by pituitary extracts opened up a road which may lead us to understand exactly how and where, not only the pituitary but also the adrenal rather may have its effect.

Since corticosterone stimulates the catabolism of protein, that is, stimulates proteolysis, then it may be anticipated that this steroid may actually play some role in intracellular proteolytic enzyme action. The continuation of studies on the effect of purified hormones in specific enzyme systems will undoubtedly enable us to understand sooner those phenomena that we call clinical endocrinopathies.

What have Dr. Long's studies got to do with diabetes? It is almost repetitious for me to point out that his observations and data on the effect of corticosteroids give us the mechanism of, or at least some indications of the mechanisms which are responsible for the increased protein nitrogen excretion which occurs in diabetes. The fact that any stress situation induces increased corticosteroid secretion and consequent increase in protein catabolism makes it easier to understand the fact that the diabetic patient so readily becomes worse at almost the slightest physical or even emotional disturbance; irrespective whether the insult to the diabetic patient produces the effect by the sympathetic nervous system, or through the endocrine system or acts on the diencephalon, there is no question but that it induces increased adreno-

corticotrophic secretion and a consequent increase in adrenal cortical activity, which in turn will induce an increase in catabolism and a state which has many of the characteristics of diabetes. In the diabetic that will produce an aggravation of the existing symptoms and greater needs for insulin, which we would call exacerbation of diabetes or insulin resistance.

In a recent study we demonstrated that emotional disturbances induce hyperglycemia only in diabetic subjects, though glycosuria can be induced even in normal subjects. The work of Selye and of Long help us understand why this emotional disturbance can produce an exacerbation of diabetes in the diabetic subject, since only if homeostasis is sufficiently disturbed will we see the effect of emotional factors acting via the adrenal and pituitary on protein and carbohydrate metabolism.

I may belabor the point but I am anxious to emphasize the importance of Dr. Long's paper in giving us a better understanding of the exacerbation which occurs in the emotionally and organically disturbed diabetic, or even of the fluctuations observed in the so-called juvenile diabetic which makes his treatment so difficult.

Finally, I wish to draw your attention to another clinical phenomenon which is given some explanation. The diabetic's susceptibility to infection and his lack of resistance in general is well known with regard to disturbance. Yet nobody has been able to demonstrate why this should be the case. The studies on lympholysis, so well discussed tonight, give us an inkling of what may be happening. It is quite possible that derangement in cortical function and consequent exhaustion of the lympholytic mechanism may be the basis of the decreased resistance of the diabetic. This gains credence from the work of McCullough who observed loss in blood proteins in patients suffering from diabetes, and especially in the light of Dr. Long's observations. There is no question that the data presented tonight, as other discussers pointed out, suggested innumerable problems to be studied.

I did not hear anybody ask Dr. Long any questions, and in spite of the fact that my voice is failing I shall ask a few.

He has pointed out in the guinea pig with intact adrenals the ascorbic acid content falls under stress or the epinephrine situation, and that the ascorbic acid takes a longer time to return in the guinea pig because it cannot synthesize ascorbic acid and must get it by ingestion. Man too

cannot synthesize ascorbic acid, so the question arises: what happens in the individual exposed to stress, not to Addison's but the individual exposed to stress and presumably suffering from adrenal ascorbic acid insufficiency, will he require ascorbic acid administration?

The next question I should like to ask is, what is Dr. Long's impression as to the adrenal cholesterol and ascorbic acid content in experimental diabetes? I shall not ask him in human diabetes.

DR. LONG: Well, I think I got off very lightly. I was wondering what was going to happen when I saw the team that was lined up to discuss the paper. They have been very kind indeed and all I can say is that Dr. Mirsky spoiled the beautiful friendship growing up between us by asking questions, particularly such difficult ones to answer.

In regard to the relationship of ascorbic acid and the adrenal to stress in man, as to whether a situation could be visualized in which as a result of continued stress there would be a reduction of the adrenal ascorbic acid to a point at which the function of the adrenal is interfered with, that in itself is a question which I cannot give you an answer to. It is now possible to say only one thing and that is I think it has been fairly well established, certainly following burns in man, that the requirement of the whole organism for ascorbic acid is very greatly increased. There are, many of you know, reports of the ingestion of a half or one gram of ascorbic acid a day in these circumstances without practically any of it appearing in the urine. That is not to say all is being used by the adrenal. It would be very difficult to say exactly how much the adrenal is using. All I can say is if it can be shown that ascorbic acid is definitely and essentially concerned with the elaboration of cortical secretion, the possibility does exist in species in whom there is inability to synthesize ascorbic acid to form a secretion adrenal insufficiency might occur if the condition were pushed to a point where the gland was entirely deprived of vitamin. I don't know of any work which has been done on this point.

I can only say we have made an approach to the problem. It is far from complete at the moment. This was done to find out in the guinea pig in which scurvy is produced, as to what its reactions are to many of these situations. The study has not gone forward enough yet but it can be, I think, said there appears in this vitamin deficiency in the guinea pig in contrast to other vitamin deficiencies a specific relationship between the hypertrophy of the adrenal which occurs and the lack of the

vitamin. This much I do know, that the hypertrophy of the adrenal is not an inanition phenomenon as in thiamine deficiency. It appears to be definitely related to lack of vitamin. Obviously one can go on from that point. I am sorry we have not gone on to give you a very good answer to that question.

Strangely enough, and I am sure Dr. Mirsky will think it rather strange, we have never determined the ascorbic acid and cholesterol content in an experimental diabetes. Perhaps now that Dr. Mirsky has raised the point he ought to do the experiment.

I thank you all very much for listening to me so kindly and thank the New York Diabetes Association for asking me to speak this evening.

CHAIRMAN ROSENTHAL: I am sure we are all looking forward next year to learning what the content of cholesterol and ascorbic acid is in the adrenal in diabetes.

THE DIAGNOSIS AND TREATMENT OF CONGENITAL CYANOTIC HEART DISEASE*

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GENERALIZED cyanosis is a sign of the presence in the arterial blood of sufficient reduced hemoglobin to impart a dusky color to the skin and mucous membranes. It is always due either to a return flow of inadequately oxygenated blood from the lungs, or to mixing of the venous and arterial streams within the heart. Since both of these conditions are present throughout fetal life, it follows that the normal fetus is always cyanotic. In the fetus partially oxygenated blood from the inferior vena cava mixes with pure venous blood from the superior vena cava in the right auricle, from there it passes either into the right ventricle, or through the foramen ovale and left auricle, into the left ventricle. The ventricular blood flowing outward through the aorta and that flowing through the pulmonary artery is in both cases mixed venous and arterial, and since the two streams join almost immediately at the junction of the ductus arteriosus with the aorta, there, is, in effect, no difference between them. It is not surprising, therefore, to find that developmental abnormalities in the separation of the right heart chambers from the left may offer no serious handicap to fetal development. They affect the child adversely for the first time after birth and the establishment of pulmonary respiration, and then only if the defect is such that a large proportion of the blood which enters the heart can flow out through the aorta without having first passed through the lungs.

Separation of the heart chambers normally occurs early in fetal life by the upward growth of the interventricular septum to join the septum formed by longitudinal division of the primitive truncus arteriosus into two vessels of equal size, the aorta and the pulmonary artery. If this

* From the surgical services of the Presbyterian and Babies Hospitals, and the Department of Surgery, College of Physicians and Surgeons.
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division is unequal, the septum cannot become complete since the base of the larger artery will straddle it. If the larger artery is the pulmonary, blood from both ventricles will pass into the lungs. but the blood which passes out through the aorta will be entirely arterial and no cyanosis will result. If, on the other hand, the aorta is the larger, blood from both ventricles will pass into the systemic circulation, resulting in cyanosis. Cyanosis will also result if the ventricular septum develops so poorly that a large defect remains which permits free ventricular mixing, even though the division of the truncus arteriosus has taken place normally.

These are the most frequent causes of cyanosis due to cardiac maldevelopment, but they are by no means the only possibilities. The interauricular septum normally remains open, through the foramen ovale, until birth. The change in pressures which then occur as a result of the sudden opening of the pulmonary vascular bed normally cause functional closure, but if there is any obstruction to the flow through the right heart, venous blood may continue flow from the right auricle into the left with a resulting mixture of venous and arterial blood in the left ventricle and aorta. Finally, a variety of bizarre abnormalities of the great vessels, especially the pulmonary veins and vena cava, may result in shunting of venous blood into the arterial circulation.

It is not the purpose of this discussion to describe or enumerate all of the abnormalities which may result in cyanosis, but rather to call attention to the features common to those which, as a result of the recent work of Blalock and Taussig, can be helped in some measure by the establishment of a compensatory shunt by operation. If cyanosis is the result of free mixing of venous and arterial blood in the heart, there is at present no compensatory circulatory adjustment which the victim of such an anomaly can make, and none which can be created for him by operation. If, however, the cyanosis is influenced by an obstruction to the flow of blood into the lungs through normal channels, development of a collateral flow may do much to offset it.

Three types of collateral may occur in these patients. The first results from the fact that blood normally enters the lungs not only through the pulmonary artery but also through the bronchial arteries. When the former channel is greatly restricted the latter dilates, sometimes to a remarkable degree. The lung hilus may then be the site of a mass of small tortuous vessels, originating from the aorta, through

which enough blood can pass to maintain life even when the pulmonary arterial channel is virtually completely blocked. The second form of collateral is less effectual, but is usually present to some degree, and, like the first, probably increases as the patient grows older. This consists in the development of new channels, both venous and arterial, which cross from the systemic circulation to the lung through the development of adhesions between the mediastinum and chest wall and the lung. The third and most effective collateral will result if the ductus arteriosus remains patent. This vessel, which in fetal life carries blood from the pulmonary artery to the aorta, allows blood to pass in the opposite direction when it fails to close at birth. Depending on its size, a more or less large proportion of the blood passing out through the aorta will pass back into the lungs and this may act as a very effective collateral if there is a block in the pulmonary artery. If, then, this channel tends to close, or fails to increase in size as the child grows, compensation will become progressively worse, cyanosis will deepen, and ultimately death may follow.

Knowledge of the existence of this type of collateral is not new, but Taussig[1] was the first to suggest that a collateral of the same type might be produced surgically, and the brilliant work of Blalock[2] has proved the correctness of her view. By bringing the proximal end of a large vessel originating from the aortic arch, either the innominate, one of the subclavians or one of the carotids to the side or distal end of either pulmonary arterial branch, the surgical equivalent of a large patent ductus can be created. Such a shunt has been used in animals by Eppinger, Burwell and Gross[3] to study the effects of ductus patency and was shown by them to divert a large amount of blood into the lung. It is a technically difficult operation to perform and its effectiveness depends on the existence of a pulmonary vessel of sufficient size to permit it, a situation which is not always present. It also may be prevented by anomalies of the aortic arch and great vessels, but when it can be carried out, the effectiveness of the creation of such a new collateral shunt may be dramatic.

How, then, can we distinguish those abnormalities which can be relieved? When the aorta overrides a small, high septal defect and the pulmonary artery is poorly developed, blood entering the right ventricle may leave either through the aorta or through the pulmonary artery. In these cases there is frequently a very narrow and rigid stenosis of the

latter. As a result the right ventricle becomes enlarged and hypertrophied and the systolic pressure developed within it is high even at rest. The amount of blood passing through the stenotic pulmonary artery at rest is, in those children who survive the neonatal period, enough to sustain life, but its proportion to that which passes through the aorta varies with the total amount which enters the heart. Thus any increase in flow will cause a large proportion of blood to flow from the right ventricle into the aorta and cyanosis will increase. Similarly any increase in resistance in the pulmonary circuit will increase the shunt.

These individuals will, then, show a degree of cyanosis at rest which reflects the severity of the pulmonary block. It may or may not be conspicuous. With exertion or with excitement, and especially with crying, the cyanosis rapidly deepens so that the child becomes extremely dyspneic and may even lose consciousness or develop convulsions. There is usually a harsh systolic murmur over the base of the heart, the character and site being variable. On x-ray the heart shows enlargement of the right ventricle, but not much general enlargement, and a concavity in the region of the pulmonary artery. The electrocardiogram shows right axis deviation. This is the combination known as the Tetrology of Fallot.

With time, compensatory polycythemia develops, increasing the oxygen carrying capacity of the blood, but also increasing its viscosity. This increased viscosity then further slows the flow through the narrowed pulmonary opening and contributes a further element of block, so that a vicious cycle is established. In extreme cases this may result in spontaneous thrombosis, especially in the cerebral vessels. In others acidosis from incomplete oxidation in the tissues or loss of carbon dioxide due to hyperventilation may occur. Similar symptoms and physiologic disturbances will result from other anomalies in which an intracardiac right to left shunt is increased by pulmonary vascular block, though the shape and size of the heart will be different, and the murmur and changes in the electrocardiogram may vary greatly.

When cyanosis is due to mixing without pulmonary block, it may be severe but will vary less. Exertion will cause dyspnea, and exercise will be limited by the ability of the circulation to carry oxygen to the tissues, but an increase in cardiac output will not change the proportion of mixing so extreme evidences of acute oxygen lack will not be evident. Such patients may show great enlargement of the heart, but it

will be less asymmetrical, and the pulmonary arterial shadow will often be prominent. Murmurs may or may not be present, and the electrocardiogram will not as often show right preponderance.

The degree to which these changes are present is extremely variable. When it is extreme, the evidences of pulmonary block are clear, but in individuals less severely affected the distinction is frequently difficult. It is in such cases that studies by the method of intracardiac catheterization developed by Cournand and Ranges[4] are especially valuable, not only in establishing the nature of the anomaly, but especially in determining whether shunting of peripheral blood into the pulmonary circulation can be expected to alleviate the symptoms.

During the past two years twenty-eight patients have been studied at the Columbia-Presbyterian Medical Center as possible candidates for operation. Of these, 16 have been operated upon, and 12 were rejected, because it was believed that a shunt would not help them. In seven of these intracardiac catheterization studies were done my Doctors Baldwin, Greene and Mathers. A detailed description of the method and analysis of the data is not suitable here. In general, the method consists of introducing a catheter into the right auricle, where pressures are recorded and from which a sample of blood is withdrawn. The catheter is then passed into the right ventricle and, if possible, into the pulmonary artery. In some cases anomalies have permitted it to pass also into the left auricle, pulmonary veins, and left ventricle. Each position is checked fluoroscopically, and pressures and blood samples are taken from each site. Analysis of the data will then give direct information on the pressure relationships of the various chambers and the degree of mixing of arterial and venous blood in each. By using this data in combination with simultaneous determination of oxygen consumption in the lungs, and oxygen content of the arterial blood (obtained from the femoral artery) the peripheral blood flow can be calculated indirectly by the Fick principle. This can then be compared to similar indirect calculation of the pulmonary blood flow by assuming 95 per cent saturation of the pulmonary vein blood. With this information the type of anomaly can be deduced with, we believe, reasonable certainty.

By this method the seven cases which were studied and considered unsuitable for operation were analyzed as follows:

Case 1: An adolescent deaf mute permitted sampling from all four

cardiac chambers, proving the presence of a patent foramen ovale. The right ventricular blood contained more oxygen than the right auricular, but less than the blood in the left ventricle; this, in turn contained less than the left auricular blood. The blood in the peripheral artery was intermediate between that in the right and left ventricles. Thus mixing in the ventricles was present which was the cause of his cyanosis. This conclusion was further confirmed by the fact that his pulmonary blood flow was calculated between one and three times that of his peripheral. It was concluded that no operation would help.

Case 2: A Bermudian colored boy, at first was thought to be a case for operation because x-ray and electrocardiograms indicated a Tetrology of Fallot. The right ventricular blood contained more oxygen than the auricular, but less than the peripheral blood. showing a left to right shunt through a ventricular septal defect, with the aorta receiving most of its blood from the left ventricle. Furthermore the pulmonary arterial blood at the point of bifurcation was identical with the aortic, demonstrating the presence of a compensating patent ductus arteriosus. The pulmonary blood flow was almost identical with the peripheral, proving that the shunt provided by the ductus was adequate in volume. so that no further advantage would be gained by producing a new shunt surgically.

Case 3: A child of missionary parents whose cyanosis became pronounced during their stay at a mission high in the hills of India. Her pulmonary arterial blood was almost identical in oxygen content with her peripheral, though the right ventricular blood was lower. Thus both great vessels received blood from both ventricles, indicating a large defect, an interpretation confirmed by the finding of a pulmonary blood flow over twice that of the peripheral.

Case 4: A deeply cyanotic child whose mother, a nurse, had set her heart on operative "cure." Pulmonary arterial blood was not obtained, but the finding of a pulmonary flow 25 per cent greater than her peripheral made it clear that there was no obstructive element, the cyanosis being due to a large septal defect.

Case 5: A little boy who showed only transient cyanosis. His pulmonary blood flow was over three times his peripheral, demonstrating a small septal defect with predominantly left to right flow and no obstruction.

Case 6: Another little boy with similar, though less marked, findings.

TABULAR SUMMARY

	Improved		*Post-*			
	Dramatic	*Moderate*	*Operative*	*Died*	*Total*	*Per Cent Mortality*
Right Innominate-Pulmonary: End-to-Side	1	1	..	..	2	....
Right Innominate-Pulmonary: End-to-End	..	..	..	1	1	....
Right Subclavian-Pulmonary: End-to-Side	2	2	1	1	6	....
Right Subclavian-Pulmonary: End-to-End	..	1	..	..	1	....
Left Subclavian-Pulmonary: End-to-Side	1	..	..	..	1	....
Left Subclavian-Pulmonary: End-to-End	1	..	..	..	1	....
Total Anastomoses Completed	5	4	1	2	12	17%
Anastomosis Not Completed	..	..	1	3	4	75%
Total	5	4	2	5	16	31%

Case 7: A boy who showed an increase in oxygen content of the right auricle over that in the vena cava, demonstrating the presence of an auricular septal defect with the left to right shunt, and a higher pulmonary than peripheral flow. It is possible that the auricular defect acts in this case in a compensatory manner, but it could not do so if there were any appreciable block in the pulmonary artery.

Of the sixteen cases operated upon, only two were studied by intracardiac catheterization because we prefer not to use the method in very small children. In both instances the diagnosis of pulmonary stenosis was confirmed at operation. The remaining operative cases were selected because the findings on physical examination, x-ray and electrocardiography made the diagnosis of interference with pulmonary flow reasonably certain. All of them were severely handicapped, some more than others. The diagnosis was confirmed at operation or autopsy in all but two. One of these, who died on the operating table, showed at autopsy a rudimentary right ventricle with an almost obliterated pulmonary artery. The blood stream passed from the right auricle through a large defect into the left and thence through the ventricle into the aorta. Practically all of his pulmonary flow entered the lung through collaterals of the bronchial artery, and when these were divided in exposing the pulmonary artery for anastomosis, acute anoxemia and death occurred. The other showed a pulmonary artery of normal size, and

though an anastomosis was successfully accomplished it is doubtful whether he will show much improvement.

Five patients died, an over-all mortality of 31 per cent, two on the operating table and three postoperatively. In two of these the anastomosis was successfully accomplished and death was due to errors in postoperative care. In the other three, including the two who died on the table, death was presumably due to anoxia which resulted from dividing collateral to the lung without providing the more effective anastomotic collateral. In the remaining thirteen cases, anastomoses were accomplished in all but one. This boy proved to have an anomaly of the great vessels of the aorta such that no large peripheral artery could be found for anastomosis. He has recovered from operation and it is possible that a second attempt on the opposite side may prove successful.

The type of anastomosis to be performed cannot always be determined beforehand but must depend in part on the anomalies encountered, in part on the amount of flow it is desired to create. Thus Blalock[5], in 246 cases, has performed right subclavian to pulmonary, end-to-side in 150, other end-to-side anastomoses in 57, and other procedures in 39, with an over-all mortality of 21 per cent.

In our experience, successful completion of an anastomosis has resulted in dramatic improvement in 5, moderate improvement in 4, the remaining one being too recent to be sure. Those who have been improved dramatically have changed from miserable little things who could hardly walk across a room without having to squat for breath, or who had to be carried, into children who, though limited in exercise tolerance, can lead a fairly normal, if restricted. life. They show little or no clinical cyanosis, their polycythemia is much less, and they have begun to lose the clubbing of fingers and toes. Those in whom improvement was less dramatic were, in general, less restrictd to begin with. Their exercise tolerance is better and their cyanosis is less. It must be emphasized, however, that restitution to normal is never accomplished and that the ultimate course remains in doubt. It seems probable that many will ultimately succumb to circulatory failure, as in the case of uncomplicated patent ductus, and the threat of subacute bacterial endocarditis is probably increased by the procedure. These liabilities, together with the uncertainties of diagnosis, the technical difficulties of the procedure and the poor surgical risk that these patients present must

temper our enthusiasm in recommending operation, and restrict its use to those patients whose prognosis is otherwise hopeless; for these, however, it offers real hope in an otherwise desolate outlook.

Summary

The physiologic and anatomic abnormalities which are found in cases of congenital anomalies of the heart associated with cyanosis have been discussed. It has been brought out that in certain cases the establishment by operation of a shunt between the peripheral and pulmonary circulation, as demonstrated by Taussig and Blalock, may do much to relieve the symptoms. The problem of selection of those cases which can be helped by operation is explored and the usefulness of intracardiac catheterization studies is demonstrated by citing seven cases studied by Baldwin and her co-workers in whom it was demonstrated that operation would not be useful. Sixteen cases are reported in which operation was done in an attempt to produce a new collateral shunt, of which some type of anastomosis was accomplished in twelve. The over-all mortality was 31 per cent, and in those in which the anastomosis was accomplished it was 17 per cent. The operation resulted in dramatic improvement in five severely handicapped children, in four the improvement was moderate. The risks and limitations of the procedure are brought out, as well as its great usefulness in selected cases.

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STUDIES IN NEW ANTICONVULSANTS*

H. Houston Merritt and Charles Brenner

Introduction

Approximately ten years ago, while working with Dr. Tracy J. Putnam in Boston, the conclusion was reached that all of the physiological and biochemical studies which had been made up to that time on patients with seizures, had not brought us to the solution of the problem of the causation of seizures; nor had these studies resulted in any significant advances in our methods of controlling or reducing the number of seizures in patients with symptomatic or idiopathic epilepsy. In fact, there had been no progress in the medical treatment of patients with seizures since 1912 when Hauptmann introduced the use of phenobarbital. It was, therefore, decided to approach the problem from a different angle by making a systematic study of the anticonvulsant activity of a large number of chemical compounds.

Methods: The method of testing the anticonvulsant action of a compound which was in general use at that time, namely, protection against convulsant drugs, was cumbersome, costly, and unreliable. In addition, it was thought that the convulsions resulting from electrical stimulation of the cerebral cortex were physiologically more closely related to the spontaneous convulsions in humans than those produced by convulsant drugs. An apparatus[1] was devised by which a direct current could be passed through the head, between two electrodes, one of which was placed on top of the skull and the other in the animal's mouth. Cats were selected for test subjects because of their availability and the convenience in handling. It was shown that the amount of current, as measured in milliamperes, necessary to produce a convulsion in a given animal, was remarkably constant on repeated testing during one day or on different days. It was also shown that drugs, such as phenobarbital or bromides, which were known to reduce the frequency of seizures

* From the Division of Neuropsychiatry, Montefiore Hospital and Department of Neurology, College of Physicians and Surgeons, Columbia University.
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in many patients with epilepsy, were effective in raising the convulsive threshold to electrical stimulation in cats. Conversely, it was also shown that a procedure which increased the frequency of seizures in epileptics, such as excessive hydration by the exhibition of pitressin parenterally and water by mouth, caused a lowering of the threshold to the electrical stimulation in the animals.

A number of chemical compounds were selected for testing on the basis of the similarity of their structural formulae to that of known anticonvulsants. Various pharmaceutical manufacturers also were invited to submit for testing all compounds which could conceivably have an anticonvulsant action.

By this method, it was possible to make a preliminary screening[2] of a large number of compounds (over 700). A few of the compounds which were found to have a high degree of protective action against electrically induced convulsions, were selected for further studies in animals to determine whether they could be considered suitable for clinical use in patients subject to convulsive seizures. These studies included chronic tests in animals to determine whether continued daily administration of the compound would result in a maintenance of a high level of resistance to electrically induced convulsions and administration of the compound to various animals (mice, cats and dogs) for periods of several months to determine whether toxic changes would result from long continued administration.

Results: Approximately 10 per cent of the 700 compounds were found to produce a significant elevation of the convulsive threshold in the acute experiments (Table I). While it has not been possible to determine the exact chemical radical or radicals which are effective in raising the convulsive threshold, the effective compounds fell into six main groups: barbiturates, benzoxazoles, hydantoins, ketones, oxazolidinediones, and phenyl compounds with sulphur.

Unfortunately the laborious and time consuming nature of the preliminary testings and the toxic properties and unpalatable taste of some of the compounds have made it impossible to carry out clinical tests, up to the present time, on more than a few of these compounds, and in only one, 5,5 diphenylhydantoin, has this clinical trial been extensive. This is due, in part, to the fact that the results obtained with this compound, which was one of the first to receive a clinical trial, were so superior to the results obtained with previous forms of medical treat-

TABLE I

LIST OF COMPOUNDS HAVING A HIGH DEGREE OF ANTICONVULSANT ACTIVITY IN ANIMALS

BARBITURATES

5-n-Butyl-5-phenylbarbiturate, sodium
Ethyl i-amyl barbital
5-Phenyl-5-ethyl barbital
5-n-Propyl-5-n-butyl-thiomethyl barbituric acid
Sodium cyclopentenyl allyl barbituric acid

BENZOXAZOLES

1-Benzylbenzoxazole
1-Methylbenzoxazole
2-(α-n-Propyl-β-phenoxy)-butyl-benzoxazole

HYDANTOINS

5-i-Amoxymethyl-5-phenylhydantoin
5-(n-Butoxymethyl)-5-phenylhydantoin
5-(i-Butoxymethyl)-5-phenylhydantoin
5-(t-Butoxymethyl)-5-phenylhydantoin
5-n-Butyl-5-(1-naphthyl)-hydantoin
5-i-Butyl-5-(1-naphthyl) hydantoin
5-Cyclobutyl-5-cyclohexyl hydantoin
5-Cyclobutyl-5-phenyl-hydantoin
5,5-Diphenylhydantoin
5,5-Di(α-thienyl)-hydantoin
5-Ethyl-5-(1-naphthyl) hydantoin
5-Ethyl-5-(2-naphthyl) hydantoin
5-(1-ethylpropoxymethyl) -5-phenylhydantoin
5-Methoxymethyl-5-phenylhydantoin
5-(2-Methyl-butoxymethyl) -5-phenylhydantoin
3-Methyl-5-ethoxymethyl-5-phenylhydantoin
5-Methyl-5-(1-naphthyl)-hydantoin
5-Methyl-5-phenoxymethyl-hydantoin
5-Methyl-5-phenylhydantoin
3-Methyl-5-n-propoxy-methyl-5-phenylhydantoin
3-Methyl-5-i-propoxy-methyl-5-phenyl-hydantoin
5-(1-Naphthyl)-5-n-propylhydantoin
5-Phenyl-5-(benzyl-mercapto-methyl) hydantoin
5-Phenyl-5-i-butyl hydantoin
5-Phenyl-5-n-butyl-mercapto-methylhydantoin
5-Phenyl-5-i-butyl-sulfono-methylhydantoin
5-Phenyl-5-cyclohexyl-mercapto-methyl-hydantoin
5-Phenyl-5-(1, 2-dimethyl-propoxy-methyl) hydantoin
5-Phenyl-5-ethyl-mercapto-methylhydantoin
5-Phenyl-5-methyl-sulfono-methylhydantoin
5-Phenyl-5-methyl-mercapto-methylhydantoin
5-Phenyl-5-n-propyl-hydantoin
5-Phenyl-5-i-propyl-hydantoin
5-Phenyl-5-n-propyl-mercapto-methylhydantoin
5-i-Propoxymethyl-5-phenylhydantoin
5-n-Propyl-5-(1-naphthyl) hydantoin
Sodium 5-ethyl-5-i-amylhydantoinate
Sodium 5-phenyl-5-phenethyl hydantoinate
Sodium-5-phenyl-5-(tetrahydropyrane-4) hydantoinate
Sodium 5-(n-propoxymethyl)-5-phenyl hydantoinate
α-Tetralonespirohydantoin

KETONES

Acetophenone
Acetophenone oxime
Acetylbenzoyl
α-Benzoin oxime
Benzoylacetone
Benzyl carbamate
Benzy methyl ketone
Benzyl methyl ketone oxime
Dibenzyl ketone
Diethyl ketone
β-Dimethylaminoethyl-2-naphthyl ketone hydrochloride hydrate
2-Furyl phenyl ketone
p-Hydroxyacetophenone
Paraldehyde
Phenyl n-amyl ketone
Phenyl n-butyl ketone
Phenyl propyl ketone
Propiophenone
i-Valerophenone

OXAZOLIDINEDIONES

5,5-Diphenyl-2,4-oxazolidinedione
5,5-Di-n-propyl-2,4-oxazolidinedione calcium

PHENYL COMPOUNDS WITH SULFUR

α-(o-Aminobenzenesulfonamido)-pyridine
2,4-Diaminothiazolyl phenyl sulfone
Ethyl phenyl sulfone
Ethyl phenyl sulfoxide
Ethyl phenyl sulfide
Propyl phenyl sulfoxide
i-Propyl phenyl sulfoxide

ment, that it has been the custom to administer other compounds only to those patients whose seizures were not relieved by 5,5 diphenylhydantoin. This procedure does not give a true index of the clinical anticonvulsant activity of the other compounds but rather measures their effectivity in patients who have been refractive to 5,5 diphenylhydantoin and also to previous forms of therapy, including phenobarbital, mebaral and the bromides. This procedure was considered justifiable, however, since the object of the study was to find the most efficient anticonvulsant, and not merely a substitute for a previously established anticonvulsant. The study is still in progress and new compounds are being tested as soon as the chronic toxicity studies indicate that they are suitable and pharmacological methods of large scale production are available. This report will deal with only those compounds which have been given a fairly extensive trial to date.

*5,5 Diphenylhydantoin**: The results obtained in the treatment of 200 patients with sodium 5,5 diphenylhydantoinate (dilantin sodium, phenytoin sodium) were reported to the American Medical Association at their meeting in 1938 by one of the authors and Dr. Tracy J. Putnam.[3] Further experience with this compound in a large series, was reported in 1940[4] and 1942[5]. The efficacy of sodium 5,5 diphenylhydantoinate in preventing convulsive seizures in humans, has been confirmed by many observers[6] and it is now generally recognized that it is the most effective agent for the prevention of grand mal and psychomotor seizures that is available at the present time.

In spite of the excellent results which have been obtained with sodium 5,5 diphenylhydantoinate in grand mal and psychomotor attacks, it does not have any appreciable effect on petit mal or prevent the occurrence of grand mal or psychomotor seizures in all patients. In addition, the administration of an effective dose is not possible in some instances due to the development of untoward side reactions (ataxia, nystagmus, gastric distress, skin rashes and hypertrophy of the gums).

*5 Methyl, 5 Phenyl Hydantoin**: 5 methyl, 5 phenyl hydantoin was administered to forty-one patients for periods ranging from five days to one year. All of these patients had previosuly been treated with various anticonvulsant drugs, including 5,5 diphenylhydantoin, phenobarbital and mebaral, either alone or in combination and they had not been re-

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE II

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF 5-METHYL-5-PHENYLHYDANTOIN TO 41 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Entirely Controlled	9
Reduced in Frequency	10
Increased in Frequency	1
Frequency Unchanged	6
Insufficient Observation	15*

* In the majority of these patients, treatment was discontinued after a few days because of skin rash.

lieved of their seizures by these forms of medication.

This compound was administered to twenty-six of the forty-one patients for a sufficiently long period to evaluate its anticonvulsive activity. The attacks were entirely controlled in nine (35 per cent), reduced in frequency in ten (38 per cent), unchanged in six (23 per cent), and increased in frequency in one (4 per cent) (Table II). In the remaining fifteen patients, the anticonvulsant activity of the compound could not be evaluated because of the occurrence of an allergic dermatitis in fourteen and gastrointestinal symptoms in one patient.

With regard to the type of seizures, the beneficial effect of this compound was greatest when the seizures were of the grand mal or psychomotor type. The compound was administered to only a few patients with petit mal seizures and in one of these, the attacks were increased in frequency.

A skin rash developed in fourteen of the forty-one patients (34 per cent). In twelve of the fourteen patients with this reaction, the rash was of a scarlatiniform or morbilliform nature and appeared five to ten days after starting the treatment. The rash recurred with readministation of the drug in all but one case. In two patients the rash took the form of an exfoliative dermatitis which appeared after about ten days of use of the drug. In one of these patients there was also a severe eosinophilic reaction in the blood with displacement of the red cells in the bone marrow and a severe anemia. There were no fatalities and no

TABLE III

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF 5-I-PROPOXYMETHYL-5-PHENYLHYDANTOIN TO 25 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Transient Reduction of Frequency of Seizures	5
Frequency Unchanged	20

other serious side reactions encountered with the use of the drug in doses varying from 0.4 to 1.0 gram daily, with the exception of a mild degree of gastric distress in three patients. In particular, there was no hypnotic action, ataxia or gingival hyperplasia.

The results obtained with the administration of 5 methyl, 5 phenyl hydantoin, indicate that it has an anticonvulsant activity equal, or superior to that of 5,5 diphenylhydantoin or phenobarbital since the seizures were either controlled or reduced in frequency in nineteen of the twenty-six patients (73 per cent), who had previously been treated with the latter drugs.

It is evident that this compound merits further trial, particularly if it can be prepared in a form which can be administered without so high an incidence of allergic skin reactions.

5-Isopropoxymethyl-5-phenylhydantoin:* This compound[7] was administered for periods varying from one to three months' duration to twenty-five patients (Table III) whose seizures were not controlled by phenobarbital and 5,5 diphenylhydantoin. The administration of this compound did not result in any significant change in the frequency of seizures, either when it was administered alone or in combination with their previous forms of therapy. There was a transient reduction in the frequency of the attacks in a few patients but this improvement was not maintained. There were no toxic side effects noted from the administration of this compound in dosages varying from 0.4 to 2.0 grams daily in this small number of patients. Hypertrophy of the gums, which was present in one patient previously receiving 5,5 diphenylhydantoin, receded while the 5-isopropoxymethyl-5-phenylhydantoin was being administered.

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE IV

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF 5,5 DIPHENYLENE HYDANTOIN TO 43 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Entirely Controlled	5
Reduced in Frequency	7
Frequency Unchanged	24
Insufficient Observation	7

*5,5 Diphenylene Hydantoin**: 5,5 diphenylene hydantoin (diphenylene diimide; diphenylene glycolyl urea) was given to forty-three patients with convulsive seizures for a period varying from two weeks to thirty-five months (average six months). The anticonvulsant activity could be evaluated in thirty-six of these patients. In the remaining seven patients it was not possible to estimate accurately the anticonvulsant effect of the compound either because prolonged administration was prevented by the appearance of a toxic skin reaction or because follow-up data were inadequate or unreliable.

In thirty-one of the thirty-six patients, seizures had not been controlled by various other forms of therapy and in five, the 5,5 diphenylene hydantoin was the first form of therapy. The results obtained in these five patients, plus the thirty-one patients refractory to other forms of therapy, are shown in Table IV.

In the thirty-one patients who had been treated with phenobarbital and dilantin, the attacks were entirely controlled in three (8 per cent), greatly reduced in frequency in five (14 per cent), and not significantly affected in twenty-three (78 per cent). The reduction in frequency of attacks, when present, was in grand mal or psychomotor equivalent attacks. No effect was noted in the frequency of petit mal attacks in the three patients in this group who were subject to this type of attack.

In the five patients who had not received any adequate treatment previously, there was complete remission of attacks in two (both of whom had frequent petit mal and grand mal attacks) and great reduction of the frequency in an additional two. In the remaining case, there

* The toxicity studies on this compound were made in the laboratories of The Wm. S. Merrell Company. We are greatly indebted to them for supplying us with the drug used in this study.

was a temporary remission in the attacks with later recurrence at their previous frequency. All five of these patients had frequent attacks and were treated with 5,5 diphenylene hydantoin for seven months or more.

The dosage administered varied between 0.4 and 2.3 grams daily. The effects of excessive dosage were similar to those seen with mild dilantin intoxication: ataxia, nystagmus, diplopia and dysarthria, without drowsiness. The majority of adults were able to take 1.7 gm. daily (the usual maximum dose) without developing these symptoms, although an occasional patient could not. One patient took 2.3 gm. daily regularly for months without ill effect.

Seven patients of the forty-three (16 per cent) developed an allergic dermatitis while taking 5,5 diphenylene hydantoin and in one patient this diagnosis was made but was later considered doubtful. The time of onset of the rash varied from eight to twenty-one days after the first dose (average ten days). The rash was usually morbilliform, occasionally scarlatiniform, and was often accompanied by fever, headache, malaise, nausea and vomiting. No patient developed exfoliative dermatitis. In four of the seven patients, administration of 5,5 diphenylene hydantoin was resumed after the rash had disappeared. Three of these four patients were then able to continue taking 5,5 diphenylene hydantoin regularly and in adequate dosage without further difficulty, while in the other patient there was prompt reappearance of toxic symptoms necessitating withdrawal of the drug again. No patients died from any cause while taking 5,5 diphenylene hydantoin.

From our limited experience with this compound, it was concluded that it had a definite anticonvulsant activity but that it was not clearly superior to phenobarbital and 5,5 diphenyl hydantoin in refractory cases. In order to determine better its anticonvulsant efficacy in comparison to phenobarbital or 5,5 diphenyl hydantoin, it should be tested in a larger group of patients not previously shown to be refractory to those drugs. The compound has no hypnotic action and the toxic side effects of the drug are not serious although the incidence of allergic dermatitis is relatively high.

*Ethyl Phenyl Sulfone**. Twenty-five patients were given ethyl phenyl sulfone[8] for periods varying from one week to seven months. All patients had been previously treated with adequate doses of pheno-

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE V

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF ETHYL PHENYL SULFONE TO 25 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Frequency Reduced	4
Frequency Unchanged	21

barbital or 5,5 diphenylhydantoin alone, or in combination. The effects of administration of this compound are shown in Table V. There was a reduction in the frequency of attacks in four, and no appreciable change in frequency in twenty-one. Complete relief from attacks was not obtained in any of the twenty-five patients, although a combination of ethyl phenyl sulfone, and 5,5 diphenylhydantoin or phenobarbital was tried in seventeen of the twenty-five patients.

There were no significant toxic side effects from the administration of ethyl phenyl sulfone in the dosages used, i.e., 0.6 to 1.6 grams daily. In three patients there was a slight degree of ataxia when taking over 1.0 gram daily.

SUMMARY

Over 700 chemical compounds have been tested for anticonvulsant activity in animals. Approximately 10 per cent of these demonstrated a high degree of anticonvulsant activity by these tests.

Only a few of these compounds have been given a clinical trial in patients with convulsive seizures. One of these, 5,5 diphenylhydantoin, has proved to be the most effective anticonvulsant yet discovered. None of the remaining compounds which has been given a clinical trial has proved superior to 5,5 diphenylhydantoin, with the possible exception of 5 methyl, 5 phenylhydantoin. This latter compound is not as yet suitable for general use on account of its toxic side effects.

Additional chemical compounds are being tested for their anticonvulsant activity in animals, and a clinical study of a larger number of those compounds which have an anticonvulsant activity in animals is in progress.

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INTRINSIC ASTHMA*

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IN the beginning all *was* allergy that wheezed, and if the methods peculiar to allergy could not reveal the cause, these methods were deemed faulty. It was recognized, however, that the simple allergic process could be aggravated and continued by secondary infections. Still later, primary infections came to be regarded as the cause of asthma—particularly when patients were found to have no trouble except at the time of a new head cold. They were said to have "bacterial allergy."

More recently chronic focal infections, as in teeth and sinuses, have been recognized as quite sufficient to explain chronic asthma.

The study of end results has led to the study of the clinical classification of asthmatic patients. The fact that these classifications, made by different workers, are all a little different, and that classifications made by the same worker at different times are also different indicates that no classification is really satisfactory. Within the past year or two, however, it has been possible to develop a simple classification of asthma which has been proved to be of considerable practical value in the clinic. The age of onset appears to be of real importance. On the one hand there are many patients whose asthma begins in childhood or in the teen ages and is evidently related quite closely to changes in season or environment. A careful history shows that the asthma comes and goes in certain places or occurs only at certain times of the year or, more rarely, depends upon the eating of certain foods. Allergy seems to be a satisfactory explanation for the cause of trouble and the diagnosis of this depends upon the history. Skin tests are helpful, but when one finds many positive skin tests with no history to go with them, and when the patient knows well of his or her sensitiveness to cats, for example, but still has no skin test to cat hair extract, one has to recognize that the skin tests have their limitations.

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The prognosis in this early allergic group is good. A goodly number of these young people have outgrown their asthma entirely, and in the others their freedom from asthma depends upon their success in avoiding the exciting agent or perhaps in being protected against it by desensitization. In this group of simple allergic asthma, the problem is not too difficult and the mechanism is reasonably clear.

"*Asthmatic Bronchitis.*" In some of these young people the asthma occurs only with new colds and one can show quite often that when the family dog or the feather pillows are removed then new colds are no longer accompanied by wheeze. In this way one can show that the disturbance has two factors; the new cold to precipitate the attack and at the same time to lower the threshold to make a slight allergy effective. The elements of infection and of allergy are both present and the treatment here has two objects. One is directed toward the basic allergy, the other toward the prevention of new colds, mostly by trying to improve the general condition of the patient. Vaccines may be helpful.

Vasomotor Rhinitis Leads to Asthma. There is a special group of these young people in which the symptoms are so characteristic and so severe that the group seems to constitute almost a special disease entity. Here are people, mostly women, who in their middle twenties develop a chronic vasomotor rhinitis which this time is severe and persists. It bears no relation whatever to changes in season or in environment, or to food. All skin tests are negative. The symptoms do not respond to treatment. After two or three years a wheeze—asthma—is added to the picture and like the nasal symptoms this wheeze is persistent and soon it becomes severe. A number of these young women have died in an attack of violent asthma and at autopsy have shown the typical sticky plugs which occlude all the bronchi. A report of these special cases is in preparation.

* * * * * *

The older group of asthmatics is of great practical importance, and it is more interesting if only because we do not know so much about it. In times past I have called the asthma in these cases "intrinsic," and for the reason that the clinical history shows that whatever the cause of trouble, it is something which the patient carries with him through all seasons and in all places, including the hospital ward. Environmental factors as well as specific foods play no part. One can anticipate, and later show that all skin tests are negative.

The causes of trouble in these intrinsic cases are numerous. "*Bacterial allergy*"—a sensitiveness to some particular organism or to the products of its growth in the body—is a theory easily suggested by the findings in the extrinsic group. Unfortunately, however, bacterial allergy can not be demonstrated by skin tests which ought to show a typical wheal and erythema reaction. It is true that vaccines and toxins will produce red inflammatory reactions appearing in 24 hours, but such reactions are not specific. One can obtain them with similar vaccines and toxins made with the cultures from other sources beside the patient himself.

"*Depletion*" was described by me last year;[1] a broad term which indicated that the asthma was due to a burden of somatic or psychic diseases, or perhaps by both factors together. Selye's[2] Adaptation Syndrome with the alarm proper, including the shock and counter shock stages, followed by resistance and finally exhaustion, appears to fit fairly well. The point is that treatment of the patient as a whole without too much attention to his asthma has brought good results.

"*Polypoid Sinusitis with Asthma*" has appeared to include a particularly difficult group of patients whose asthma is closely associated with lesions of the nose and sinuses. Further study confirms the early impression that the nasal lesions are part of the picture and not a cause of it. In the first place, more careful examination will show that turgescence of the nasal membrane, or thickening of the sinus linings is almost universal in asthma, and secondly, the end results do not show that patients with more obvious lesions behave any differently in the long run from those whose nose is relatively clear.

Emphysema occurs as a part of every asthmatic attack, but the acute process is reversible. There is, however, a special group of cases whose emphysema is primary. Why or how it develops is quite unknown. The symptoms are much like those of asthma with one interesting exception. In emphysema the nights are good—"emphysema sleeps well." In asthma, however, the nights are bad. The distinction is simple and often useful.

Finally, *Tumors and foreign bodies* must never be forgotten for they, too, can simulate all the symptoms of "asthma."

* * * * * *

Such a classification is useful in the clinic, as said. Still, however, it does not reveal the cause of asthma.

My father was a lawyer. He asked me one day, "Don't you ever

cure your patients?"—"If you do, why don't you find out how you did it?" I have been trying ever since to find the answer to that question.

Studies of end results should be helpful. Gross figures for end results in Intrinsic Asthma, arranged according to the age and decade of onset show that 20 per cent of the patients are "cured" and this figure applies roughly to all the age groups. Improved are 24 per cent and unimproved only 8 per cent. Deaths from asthma itself occurred in 13 per cent, but the figure is higher for the younger groups, just as deaths from causes other than asthma are higher for the older groups. These gross figures, however, do not mean too much. Whereas the number of cases is large in the clinical sense, it is still too small for statistical purposes.

Special study of the "cured" cases reveals a number of interesting points.

The reasons for cure, appraised partly by the patient and partly by the family doctor, vary widely. In several cases it was our treatment with vaccines, usually in combination with potassium iodide, together with protective measures, including ephedrine and adrenalin, which started the patient in the right direction. The list, however, includes other statements. Asthma disappeared when divorce was arranged; it cleared when the menopause was finally completed; when the obesity was treated; and then in other cases it was simple directions about decent living which were of great value. The woman was always tired; her diet was poorly arranged; life was hectic; emotions were near the surface; and when these things were cleared, her asthma disappeared. In other patients, and in men more than women, it was the removal of a focus of infection which seemed to do the trick. The extraction of abscessed teeth has, in certain cases, been all that was required to change the patient from a hopeless invalid to a reasonably healthy and useful person.

Sinus operations are always interesting, and the tabulation shows that in a few cases sinus surgery was in fact followed by a "cure" (in quotation marks). On the other hand, the tabulation shows also that in a larger number of cases it was the sinus operation made originally to relieve a chronic infection, perhaps with polyp formation, which precipitated the development of severe asthma. Sinus surgery still remains as a difficult and very troublesome problem.

In certain instances the "cure" which persisted, perhaps for as long as

ten years, was followed by a recurrence of asthma later and then after a time the state of cure returned again. This fact gives strong support to the idea that asthma depends upon a disturbance of some sort which is fundamental and which is always present. These patients have a "weak spot" which is asthma, and this "weak spot" flares under provocations of all sorts including allergy as one of the precipitating factors.

As this clinical study goes on it begins to look as though asthma is a disease and not merely a symptom. Whether this narrower concept will make us less ready to look for special causes in certain groups of cases, and so, perhaps, will make us miss something, or whether on the other hand it is proper to let our classification apply only to the exciting factors, and so to encourage the belief that asthma in the "young lady" is the same disease as asthma in the "old gentleman," is still doubtful. Surely it is hard to believe that the wheeze which comes to the young school girl for a day or two in the middle of the ragweed season is the same disease as that which develops suddenly in the tired business man or in the harassed housewife and pushes them down to the depths of depletion and despair.

The problem is still wide open: the approach to it is not at all clear.

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